

## COMPENDIUM INDEX

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# Concept paper no. 1 for EC on **MRP/DCP and post-licensing procedures for NAPs**

## DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

**Main theme:**

Simplification, streamlining of processes set by legislation

**Lead: Experts from CMDh/HMA**

**Questions to be considered (not exhaustive list, taken from EC document, only slightly amended)**

- *Increased use of multi-product procedures:*
  1. *worksharing at authorisation (e.g. multi-product applications for generics or BE study worksharing)*
  2. *mandatory variation worksharing*
  3. *SmPC harmonisation process*
  4. *New mechanisms to allow opt-in for "small" MS*
  5. *Increased flexibility to facilitate use of MRP/DCP for non-prescription products*
  6. *Permitting Art 29(1) referrals by CMS when the RMS is negative*
  7. *Possibility of allowing voting in CMDh to resolve referrals without the need to refer to CHMP*
  8. *Delete renewals*
  9. *Further reduction in national requirements (particularly those that are purely administrative)*

**Other ideas / topics**

10. *Re-classification of foreseen variations*
11. *No grouping of Extensions and variations - define extension as a new application?*
12. *Article 10b applications more than once in the same MS*
13. *European Annex IID for MRP/DCP MAs*
14. *Learning from the NVR*
15. *Allow CMS to raise PSRPH on the (lack of) ERP data*
16. *Clarify the use of MRP/DCP for traditional herbal medicinal products*
17. *Include traditional herbal medicinal products and homeopathic medicinal products in the scope of the variation regulation?*

## Recommendations for change

### 1. Worksharing at authorisation (e.g. multi-product applications for generics or BE study worksharing)

A generic/hybrid medicinal product can be evaluated under a centralized procedure or via the national or Mutual Recognition (MRP) or Decentralised (DCP) procedure, and the same product can be submitted multiple-times in different routes of evaluation. In addition to these different lines of submission, it is also very frequent that several applications, by being copies of one another, share many common elements for assessment, including the same supporting bioequivalence study. This may result in duplication of assessment, with time losses and the risk of different outcomes in the network. It is currently already possible to re-use an assessment that is already uploaded in CTS for duplicate dossiers by other RMS, however, it is difficult to identify these duplicates early enough. Also the applicants are often not aware that the same dossier is used by other applicants. In case section 4 of the Application form is not filled, cases of already assessed and authorised procedures cannot be recognised, leading to risk of duplication of work and divergent opinion in the assessment.

Many negative opinions or requests for referrals according to article 29 of the Directive at CMDh are related to deficiencies in the BE studies reported in the DC generic applications or to divergent opinions among MSs on these studies (please note that generic applications represent most of the DC ones); thus a harmonised opinion on the BE studies is necessary.

#### 1.1. Proposed solutions – in legislation

A new type of procedure resulting in a BE assessment certificate that could be used for later submission to other national/Mutual Recognition/Decentralized procedures could be created. This certificate could be obtained either prior to or after a centralised/decentralised procedure itself and should have a time-limit validation due to state-of-the art/ guidance changes. The transparency in the Assessment of the Study should be guaranteed with the availability of the Assessment Report.

Another option, which is preferred by the CMDh, could be adopting a Bioequivalence Worksharing procedure (in line with the ASMF Worksharing procedure (although with some differences) to involve more MSs in the Assessment of the BE study during the ongoing procedures to prepare an Assessment Report which could be adopted also in the future applications (both CAPs and NAPs). The advantages of the BE WS procedure would be related to the fact that the interaction will be with the Applicant instead of the CRO, because the BE study is part of the dossier. However, the RMS would be responsible for management and choice to adopt the BE WS procedure. Details on the WS procedure (the way to appoint parent/daughter, possibility for CMSs to raise comments, adoption in national procedures too etc) should be set in the future and maybe a Working Group on this issue could be considered, aimed to elaborate a Guidance. The risk of changing the Parent MS responsible for the assessment would be reduced in the BE WS compared to the ASMF WS because generally the BE study is only included in the new applications; thus there is no impact on variations.

The initial proposal could be starting with a pilot phase as it has been already done on the ASMF WS procedure.

A common repository or centralised database might need to be created to store the relevant certificates; otherwise an European Repository to collect the Assessment Reports from the BE WS could

be set, to be consulted by the EU assessors. A system related to the CTS-client could be used (please note that the ASMF repository of the ASMF WS is linked to CTS-Client). Otherwise we could consider to have some options in the CTS Client system to add and share the data there.

## **1.2. Proposed solutions – in guidance**

A network available master file on a product for PK, similar to the PKWP Part A of the PSBGLs that underpin the requirements for BE studies could be created. This file could be built up and maintained over the life-cycle of a product to 'certify' what is known about common elements (e.g. BCS, food, study design, NTI) for that product. Legislation might also be needed in addition to guidance to establish the 'PK file' concept and the roles and responsibilities for compiling and sharing the information.

Otherwise a "common" assessment report on the same BE studies to be adopted in different procedures could be taken into account too, based on a Worksharing procedure. In this case a Working Group could be considered (in line with the one on the ASMF WS) and a Guidance could be prepared to properly set the WS procedure. The advantage of the BE WS procedure could be also that it could be set without necessary legislation change because the BE study will be maintained in the dossier.

Moreover, the importance of the correct filling of section 4 in the Application Form should be stressed too. Finally, it would be helpful if guidance could be prepared to share relevant dossier information in order to avoid unnecessary double work.

## **2. Mandatory variation worksharing**

With the current Variation Regulation the possibility of variation worksharing has been established. It decreases the burden in NCAs as it avoids double work in different agencies. It is highly promoted by CMDh and HMA and is increasingly and successfully used by more and more MAHs. Especially the extension to purely national MAs in 2013 was regarded as a huge gain as it enabled MAHs to harmonise their purely national MAs in different member states with regard to the product information and the quality dossier. However, it is still only an optional procedure and some MAHs, especially of older products, refuse to make use of the worksharing, they even seem to prefer keeping their MAs disharmonised within Europe. This causes a lot of unnecessary burden to NCAs and especially generic MAAs as the different product information is always causing a lot of discussion, concerns and complaints during generic MAA procedures. Furthermore, the EU network is additionally burdened by MAHs keeping to submit purely national variations to the different NCAs, enforcing these member states each to do a single assessment. CMDh is trying to cope with these procedures especially in order to avoid further disharmonisation but not all cases are identified and the exchange in CMDh is also very resource consuming. CMDh and CMDv just implemented an amendment to the eAF for variations so that MAHs now have to include information on parallel national submissions and harmonised parts of the product information.

As the experience with the worksharing is very good from NCA and industry side it is therefore proposed to include the worksharing as a mandatory procedure into the Variation Regulation.

## **2.1. Proposed solutions – in legislation**

Amend Art. 20 of Reg 1234/2008/EC as follows:

By way of derogation from Article 7(1) and Articles 9, 10, 15 and 16, where a minor variation of type IB, a major variation of type II or a group of variations in the cases of point (b) of Article 7(2) which does not contain any extension relates to several marketing authorisations owned by the same holder, the holder of such authorisations **shall** follow the procedure laid down in paragraphs 3 to 9 of this Article

## **2.2. Proposed solutions – in guidance**

n/a

# **3. SmPC harmonisation process**

The CMDh creates a yearly list of products that are identified for the harmonisation of the SmPC via an Art. 30 referral procedure. However, it is increasingly difficult to prepare this list as the prerequisite for this exercise is that there is only one originator product approved in Europe. Very often, especially for very old products, there is no single originator so that these products cannot be included in Art. 30 procedures. But the disharmonisation of the SmPC of older products is a big problem for generic applications where each member state would like to adapt the generic to the originator licence on the local market. A harmonisation process for the originator or specific reference medicinal products could lead to an increase in harmonisation also for generics EU wide. A specific procedure for the harmonisation of generics would not be necessary as they have to adapt to the wording of the originator anyway, but could be foreseen in cases where the originator is not authorised any more. **A harmonisation process led by CMDh** would create less burden for the CHMP by Art. 30 referrals. **A voting system with majority outcome** should be implemented at CMDh level. This harmonisation process for RefMPs would extremely facilitate generic DCP applications and post-approval procedures.

## **3.1. Proposed solutions – in legislation**

Implement the Article 70 from the NVR also for human medicinal products but not Art. 71 and especially not Art. 72. The project may not be limited to products authorised only after 10/2005, it is essential to make it available especially for older products. Procedure for harmonisation of summaries of product characteristics should be exceptionally possible also for the substances where there is no originator/reference medicinal product authorised anymore.

## **3.2. Proposed solutions – in guidance**

n/a

## 4. New mechanisms to allow opt-in for "small" MS

Shortages in "small" member states is a frequent problem. Existing means to solve this problem are among others zero-day MRP/RUPs and inclusion of new CMS in already ongoing DCPs.

### Zero-day MRP/RUPs

A so-called zero-day procedure is a MRP or RUP procedure which is handled administratively, i.e. no update of RMS AR, no CMS comments, procedure start and End of Procedure in many cases on the same date, hence the name "zero-day" procedure. The zero-day procedures are used frequently to add "small" member states like CY, MT and IS as CMS in procedures as a way of quickly solving a shortage on these markets. The zero-day procedures have also been used more broadly during the coronavirus pandemic to prevent shortages in other markets as well.

Zero-day procedures are already covered by the existing legislation as it is really just a very shortened MRP/RUP. However, it might be useful to amend the legislation to further support these procedures. If the zero-day procedure could be mentioned in the legislation stressing its administrative nature it could lead member states to charge a dedicated, lower fee to act as RMS for these procedures. Today, fees in most RMS remain an obstacle that discourage applicants to run a zero-day procedure, as the RMS isn't able to reduce normal MRP/RUP fees, although the workload connected with a zero-day procedure is much reduced for the RMS.

### Inclusion of new CMS in already ongoing DCPs

CMDh has agreed to accept inclusion of new CMS in already ongoing DCPs in certain cases: Only during the clock-stop in a DCP and provided that acceptance is received before submission from both the RMS and the new CMS and that the requested new CMS is already a CMS in an on-going multiple/duplicate application.

More detailed requirements can be found in the *CMDh position paper concerning Applicants request of submission of multiple applications during ongoing Decentralised Procedures or inclusion of new CMS or additional strength(s) in an already ongoing Decentralised Procedure (DCP)*.

A new mechanism to allow opt-in for "small" MS could be to allow new CMS to be added in a DCP application during the clock-stop when the new CMS is **not** already a CMS in an on-going multiple/duplicate application. This could be allowed if justified in prevention of shortages in the new CMS and provided acceptance is received from both RMS and the new CMS. Similar conditions as for zero-day procedures could be applied, e.g. agreement between RMS and CMS not to send additional CMS comments and if there are "national" issues, these are to be resolved during the national phase.

The request to add a new CMS in the clock stop should be sent by the applicant as early as possible to allow the new CMS to receive the Day 70 RMS ARs and Day 100 CMS comments early in the clock stop in order to review the case and consider their late inclusion based on those documents.

The new CMS should as always be allowed a validation period according to the automatic validation period.

Pros/Cons (Inclusion of new CMS in already ongoing DCPs):

- + prevention of shortages in MS
- + more flexibility/possibilities for applicants to adjust to market demand

- risk of receiving CMS comments after the clock stop where there is not enough time to solve the outstanding issues which could lead to more CMDh referrals (Only in case of PSRPH)
- more RMS workload connected with the agreement to add new CMS during clock stop

### **Default inclusion of certain “small” MS in new procedures without any costs**

The idea from the European Commission to always include certain “small” MS in new procedures without any costs is not supported by CMDh. Many applicants will not have any plans to market their product in these “small” markets and for them it will be an additional burden to submit the application in these “small” MS and to maintain the marketing authorizations. For RMS it will also contain an additional workload. One of the benefits of the MRP/DCP procedures compared to the CP procedure is that the applicant can select exactly in which markets they would like to obtain a marketing authorisation.

## **4.1. Proposed solutions – in legislation**

### **Zero-day MRP/RUPs**

A more formalised zero-day procedure could be given in the legislation, e.g. no updated RMS AR as referred to in article 28.2. The procedure could be referred to as “administrative” whilst stressing that this procedure should not be the norm and it should be justified in the prevention of shortages on the market of the CMS.

### **Inclusion of new CMS in already ongoing DCPs**

To allow new CMS to be added in a DCP application during the clock-stop when the new CMS is **not** already a CMS in an on-going multiple/duplicate application may not require an amendment of article 28. It is noted that inclusion of new CMSs in such a scenario has already been done in exceptional cases under the current legislation.

## **4.2. Proposed solutions – in guidance**

### **Zero-day MRP/RUPs**

CTS could be updated to further support the zero-day procedures.

CMDh Guidance could be published based on “The Malta-Paper”, and internal document that outlines how zero-day procedures are conducted in Malta. Guidance is already published on some national websites.

CMDh guidance could include:

- CMS comments and thereby referral to CMDh are not foreseen
- minimum requirements, e.g. acceptance from both RMS and new CMS, submission of same dossier as approved in RMS
- how to handle if orphan indications are concerned



## **Inclusion of new CMS in already ongoing DCPs**

The current guidance may be updated if the possibilities to include new CMS is extended. The justification needed to add new CMS in already ongoing DCPs should be prevention of shortages.

Current guidance:

*CMDh position paper concerning Applicants request of submission of multiple applications during ongoing Decentralised Procedures or inclusion of new CMS or additional strength(s) in an already ongoing Decentralised Procedure (DCP)*

## **5. Increased flexibility to facilitate use of MRP/DCP for non-prescription products**

Guidance is given in *CMDh Best Practice Guide for authorisation of NonPrescription Medicines in the Decentralised and Mutual Recognition Procedures*.

Legal status (OTC/Rx) is a national issue and the decision to have a medicinal product on prescription or OTC is made at national level. Flexibility is in the interest of the authorities and industry to enable wider approval of products suitable for non-prescription use.

Flexibility in the approval process is in line with the Mandate for the *CMDh Non-prescription medicinal products Task Force* which includes the goal to "...enable wider approval of products suitable for non-prescription use..."

### **1 set of common English product information per strength/form**

Today only one *common* English, harmonized set of product information is allowed, i.e. 1 SmPC, 1 PL, 1 Labelling, per strength/pharmaceutical form.

Reference is made to article 8.3(j) that states:

**A** summary, in accordance with Article 11, of the product characteristics, **a** mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with **a** package leaflet in accordance with Article 59.

Reference can also be made to "the omeprazole case":

From CMDh minutes May 2020: "The TF discussed possible solutions for omeprazole applications with different legal status in RMS and CMS. The TF agreed that for omeprazole (and pantoprazole), due to the outcome of the Article 30 referral for omeprazole (June 2010) with two different SmPC/PL for omeprazole OTC and omeprazole Rx products, applicants need to submit separate applications split up per legal status. This approach is applicable to all cases when the common SmPC has a different text for OTC and Rx legal status."

The product information is a substantial part of the overall benefit/risk evaluation and a different set of product information could certainly lead to a different conclusion on benefit/risk. Therefore, it should be maintained that only 1 set of common product information is allowed per strength/pharmaceutical form.

Acknowledging the use of *one common* set of product information does however still make it possible to have Rx and OTC for the same product nationally in different Member States concerned with the same common set of product information with the only difference being the introductory statement in the PL and the posology appearing on the labelling. Thereby some flexibility is already allowed to the current system.

Further national flexibility is practiced by a number of MS today where the national OTC PL and labelling can contain *a subset* of the indications and indicated population of the Rx PL. This gives the possibility for more applications to reach a positive outcome with OTC status in these MS.

In the rest of the MS it is not possible to have Rx and OTC for the same product nationally *if* the legal status is reflected in the indications and/or posology. In those MS the applicant instead has to apply for separate Rx and OTC DCPs although the dossiers in all other relevant respects are identical.

Solutions have been discussed in recent years in the Non-Prescription Medicinal Products Task Force where it was concluded that "no perfect solution and no innovative approach has been identified that could be applied as a **common** approach. Following extensive discussions, the challenges have been identified".

However, there are different options on how to reach a more harmonised approach as discussed below.

### **Option 1: Splitting**

Splitting of a procedure as a mean of obtaining two procedures with OTC and Rx, respectively, has been discussed extensively in the past and was not considered a viable solution under the current legislation.

If splitting was described in legislation it may be a viable solution. Splitting could be defined as a special administrative change/variation with a **very** limited scope, i.e. splitting OTC/Rx, art. 50, requests from EC.

Required documentation: Statement/justification that splitting is legally necessary or that without splitting the MAH would be forced to withdraw MA(s) in MS and apply for new MA(s) for the same product to obtain separate OTC/Rx sets of product information.

If such a split would result in one procedure with only one MS this should be allowed in legislation as long as the split-out procedure is handled as a MRP/DCP and not as a purely NP. In addition, guidance should include that future variations have to be submitted by worksharing, where applicable, to keep any parts of the product information and the rest of the dossier that are not affected by the legal status harmonised.

Pros/Cons:

- + Saving NCA resources by initially running only one MRP/DCP
- + Harmonisation across products is kept as far as possible
- Administratively, a bit complicated (but workable)
- There is no national flexibility included in the proposal

### **Option 2: Two DCP procedures in parallel**

A different solution could be to describe in legislation that an applicant has to apply for separate Rx and OTC DCPs in those cases where the legal status is reflected in the indications and/or posology of

the product information. The submitted dossiers should in all relevant respects be identical and only differentiate with regard to legal status.

The Rx and OTC product information should be contained in one document with Rx as the basis and any OTC-related differences highlighted, e.g. with a separate colour, shading or framing. That one document should be submitted in both the Rx and the OTC approval procedure. In that way there will be increased transparency and clarity for all assessors involved of what is being proposed in the parallel procedure.

This solution would involve the applicant identifying MSs in advance that probably would grant OTC status. It should be possible for CMSs to opt in to the OTC procedure from the Rx procedure and vice versa. If for example only one "OTC-MS" is identified a DCP with this MS only should be allowed as long as the DCP is handled as such and not as a purely NP.

The two DCP procedures should follow the same timetable.

In addition, the MAH should commit to maintain the two procedures in a way so the approved dossiers keep being harmonised. Variations post-authorisation should be handled via Worksharing.

Pros/Cons:

- + Having the product information contained in one document with Rx as the basis and any OTC-related differences highlighted gives a good overview of the Product Information for assessors
- Administration of two procedures in parallel will require a bit more resources for NCAs and applicants (but workable)
- As the decision on legal status is a national decision it could be difficult to reach agreement on common product information for an OTC product among a group of MSs - To allow CMS to opt in to the OTC procedure from the Rx procedure and vice versa while the procedures are ongoing could create administrative problems (e.g. the fee is associated with a certain procedural number)

### **Option 3: National flexibility: one common English – two national PLs and labelling**

A flexible national approach is currently applied in some MS to approve non-prescription medicinal products also in cases where EU harmonisation of OTC product information has shown not feasible. The national OTC PL and labelling can in some MS contain a subset of the indications and indicated population of the Rx PL. The OTC PL can also include only smaller packages sizes of a product. It is often relevant for short term self-medication to have smaller packages. Of note, there is in these cases one common SmPC and only one SmPC per national language.

However, today national flexibility is legally not possible in most of the member states and can also not be reflected practically in all current national databases. It is a special handling in some member states and it has been refused in the past in the Non-Prescription Medicinal Products Task Force as a way to increase OTC flexibility at EU level under the current legislation.

It was discussed in CMDh (December 2021) if the new legislation should allow more national flexibility and explicitly make it possible to have two national sets of package leaflets and labelling at the individual MS's discretion. This is an issue that divides CMDh.

The discussion landed on the following compromise: CMDh's message to the European Commission is that the new legislation should not include changes that would prevent any MS to maintain their flexible approach neither should it force other MS to change their current practice.

In other words, we should not introduce legislation which makes it optional for member states to use it or not to use it. For those member states that would not make use of it this is foreseen to lead to a lot of discussions with industry. And for those member states that would make use of it, it is already possible today, so no change in legislation is needed.

## **5.1. Proposed solutions – in legislation**

### **1 set of product information per strength/pharmaceutical form**

In legislation it could be stated more clearly that only 1 *common* set of product information is possible for each strength/pharmaceutical form in MRP/DCP procedures.

#### **Option 1: Splitting**

Splitting of a MRP/DCP could be defined as a special administrative change/variation with a **very** limited scope, i.e. splitting OTC/Rx, art. 50, requests from EC. If such a split would result in one procedure with only one MS this should be allowed in legislation as long as the split-out procedure is handled as a MRP/DCP and not as a purely NP when it comes to variations, renewals etc.

#### **Option 2: Two DCP procedures in parallel**

If for example only one "OTC-MS" is identified a DCP with this MS only should be allowed in legislation as long as the DCP is handled as such and not as a purely NP also when it comes to post-authorisation variations, renewals etc.

#### **Option 3: National flexibility: one common English – two national PLs and labelling**

The new legislation should not include changes that would prevent any MS to maintain their current flexible practice neither should it force other MS to change their less flexible practice.

## **5.2. Proposed solutions – in guidance**

#### **Option 1: Splitting**

If the "Splitting" solution is implemented in the new legislation guidance would have to be developed accordingly.

#### **Option 2: Two DCP procedures in parallel**

The "Two DCP procedures in parallel" solution would require update of *CMDh Best Practice Guide for authorisation of NonPrescription Medicines in the Decentralised and Mutual Recognition Procedures*.

#### **Option 3: National flexibility: one common English – two national PLs and labelling**

For transparency reasons the flexible practice used by some MS could be mentioned in the update of *CMDh Best Practice Guide for authorisation of NonPrescription Medicines in the Decentralised and Mutual Recognition Procedures*. It should be emphasized that the national flexibility is acceptable only at the MSs discretion.

## **6. Permitting Art 29(1) referrals by CMS when the RMS is negative**

Currently, MAAs submitted via DCP will be automatically refused in case the RMS has a negative opinion at the end of the procedure, regardless of the opinion of the CMS. It is proposed to open up CMDh referrals to all disagreements between RMS and CMS, so that a CMS with a positive opinion could request a referral even if the RMS is negative.

In the NVR a possibility for the applicant to request a re-examination at CMDv level has been introduced. The same could be interesting also for human medicinal products. However, it should be made clear that no new documents that have so far not been submitted during the procedure may be provided for the re-examination procedure. Nevertheless, it should be considered that such re-examination procedures will put further burden on the network. In the NVR, the re-examination procedure in CMDv will end with the RMS final position in case MS fail to reach an agreement, so it is likely that this procedure will only prolong the procedure, but not change the outcome for the application. It is questionable whether it is justified to introduce this tool on the human side with regard to the very low number of refused applications. It is therefore proposed not to include this new tool for human medicinal products. The applicant will still have the possibility to appeal at national level and afterwards initiate an MRP in case of a positive outcome.

Moreover, it is more likely that an applicant would like to challenge a decision where at least some CMS are positive, than a procedure where there is consensus between RMS and CMS that the application is non-approvable. Therefore, it should be sufficient to introduce the possibility for a positive CMS to request a referral to CMDh.

### **6.1. Proposed solutions – in legislation**

Proposed amendment to Art. 29(1):

1. If, ~~within~~ **at the end of** the period laid down in Article 28(4), ~~a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it~~ **there is disagreement between Member States on whether the application can be approved, on the grounds of potential serious risk to public health, the disagreeing Concerned Member State** shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group.

### **6.2. Proposed solutions – in guidance**

n/a

## **7. Possibility of allowing voting in CMDh to resolve referrals without the need to refer to CHMP**

In the current legislation, an Art. 29(1) referral with no consensus agreement of the RMS and CMS will lead to a referral to the CHMP, even if only one CMS is negative. In the CHMP an opinion is then taken by majority if consensus can't be reached and forwarded to the Commission for the formal decision.

The review procedure in the NVR (Art. 54) is comparable to the Art. 29(1) referral procedure, with one major difference. If consensus is not reached between the RMS and the CMS during the review procedure in CMDv, the remaining points of disagreement will be forwarded directly to the Commission who will take the final decision.

As it is the NCAs of the MS who assess all MRP/DCPs and they are all represented in the CMDh, there is suitable competence and expertise available to take decisions in these matters in the coordination group and it is considered an unnecessary step to go via CHMP. Similar to the current decision-making process for pharmacovigilance referrals, the proposal is therefore to introduce a voting system at CMDh level including all CMDh members, not only the RMS and CMS of the procedure concerned. If consensus is not reached, the CMDh would forward the majority position to the Commission for the formal decision. By removing the involvement of CHMP, the referrals will be finalised in a shorter timeframe and CHMP will be unburdened.

### **7.1. Proposed solutions – in legislation**

Art 29(4)-(6) in Dir. 2001/83/EC could be replaced with a text similar to Art 107k (pharmacovigilance referrals):

**If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.**

### **7.2. Proposed solutions – in guidance**

n/a

## **8. Delete renewals**

Given the extent of the pharmacovigilance mechanisms in place (PSUR, signal detection, referrals), a complete re-evaluation of the benefit/risk is not considered necessary after five years. Every PSUR review contains a benefit/risk evaluation. It is not anticipated that any new safety issues would be identified during a renewal procedure, not having been discovered through signal detection and PSURs earlier in the lifecycle of the product, and these mechanisms should be sufficient to monitor the safety of the product. The renewal procedure has become an administrative burden for both NCAs and

companies without providing any additional benefits. It is noted that renewals have been deleted in the new veterinary regulation. It is suggested to do the same for human medicinal products, regardless of legal basis.

The deletion of renewals is also addressed in concept paper no. 13.

### **8.1. Proposed solutions – in legislation**

The text in Dir. 2001/83/EC needs to be changed. Art. 24(1-3) could be removed or if deemed necessary, replaced with a notion that marketing authorisations are valid until further notice/for an unlimited period. Also the header in section 9 of the SmPC needs to be changed in Art. 11, to remove the date for renewal of the authorisation.

### **8.2. Proposed solutions – in guidance**

n/a

## **9. Further reduction in national requirements (particularly those that are purely administrative)**

Reduction in Member States' national requirements is an issue CMDh has had focus on for many years together with a wish to be transparent about the existing national requirements.

In the following documents the current national requirements for new applications and variations/renewals, respectively, can be found:

- [https://www.hma.eu/fileadmin/dateien/Human\\_Medicines/CMD\\_h\\_/procedural\\_guidance/Application\\_for\\_MA/CMDh\\_043\\_2007\\_Rev\\_18\\_2021\\_04\\_clean\\_-\\_Data\\_requested\\_for\\_New\\_Applications.pdf](https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Application_for_MA/CMDh_043_2007_Rev_18_2021_04_clean_-_Data_requested_for_New_Applications.pdf)
- [https://www.hma.eu/fileadmin/dateien/Human\\_Medicines/CMD\\_h\\_/procedural\\_guidance/Variations/CMDh\\_197\\_2010\\_Rev\\_8\\_2021\\_04\\_clean\\_Data\\_requested\\_for\\_Variations\\_and\\_Renewals.pdf](https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_197_2010_Rev_8_2021_04_clean_Data_requested_for_Variations_and_Renewals.pdf)

If national requirements that prevent the validation of applications could be avoided or further minimized it would in many cases shorten the validation phase. For example, the validation period is 14 days for a DCP, but often it ends being longer partly due to invalidations based on national requirements. Further reduction in national requirements would simplify the work and save resources for applicants and NCAs. In the end it could lead to earlier patient's access to medicinal products in all member states concerned by the procedure.

Some examples of national requirements: Completion of national database; original signatures on different documents; local representatives/contact persons; documents in national language. The reason for these national requirements seems to be substantiated in national legislation and it may be difficult to solve the issue with an update of the EU pharmaceutical legislation. Instead it might require changes in national legislation.

A part from the above mentioned more administrative national requirements there are also national requirements concerning the product information, i.e. the Blue Box requirements for package leaflet and labelling. The Blue Box requirements are addressed in concept paper no. 12.

### **9.1. Proposed solutions – in legislation**

If the new legislation would be in the form of a regulation instead of a directive it might solve some validation issues if they come from differences in the implementation of the directive into national legislation.

However, the experience from the preparations of the New Veterinary Regulation suggests that a regulation will not solve everything in relation to avoiding or further minimizing national requirements.

### **9.2. Proposed solutions – in guidance**

n/a

## **10. Re-classification of foreseen variations**

In the NVR the classification of variations was severely amended. From the current system with variation types IA, IB and II the NVR switched to a 2-category classification with Variations requiring assessment and variations not requiring assessment. For the variations not requiring assessment a regulation has been set up including all changes falling under this category. All other changes are requiring assessment. Even if changes are considered to be acceptable as not requiring assessment they have to be handled as requiring assessment until the regulation has been updated for this change accordingly. This system goes back to the situation before introduction of the current Variation Regulation with variations requiring assessment as the default type. As in the current system the default type is IB which requires only a minor assessment the current legislation is regarded as a huge advantage for NCAs and industry as all changes not classified can be submitted as variation type IB requiring no assessment report, having shorter timetables and lower fees. To go back to the former system of only two variation types is regarded as highly less flexible and much more complex and it is strongly recommended to keep the current system of 3 variation types.

What is recommended though is to amend the classification guideline in order to include the currently approved Art. 5 recommendations into the guideline, consider the ICH Q12 guideline and to have a complete check of the document whether there are other opportunities to downgrade specific variations or to simplify the content with regard to conditions and/or recommendations. Clear guidance should be given how to handle CEP revisions and when these have to be submitted (see published Q&A by EMA – currently under discussion/revision in the network). Furthermore, it is essential that the classification guideline is updated on a more regular basis.

A database like the UPD database which is not connected with the national databases and including data that is not submitted in other ways (eCTD, CESP, eAF) to authorities is regarded as not manageable when relevant data for the same medicinal product is spread onto different databases. When it is intended to establish a database also for human medicinal products (apart from PMS in



SPOR?) it has to be regarded that it is essential that the complete lifecycle of a medicinal product has to be visible in national databases as well.

### **10.1. Proposed solutions – in legislation**

The text of the variation regulation has to be amended by deleting the veterinary medicinal products, no other changes are regarded necessary with respect to re-classification of foreseen variations.

The classification guideline should be updated according to the Art. 5 recommendations, ICH Q12 and other experiences or according to the latest scientific developments and requirements. A regular update of the classification guideline should be covered in the legislation.

### **10.2. Proposed solutions – in guidance**

n/a

## **11. No grouping of Extensions and variations – define extension as a new application?**

The grouping of variations across type IA, IB and type II is a huge advantage for the handling of variations and should remain in the current legislation as it is. However, the inclusion of extension applications, which are new applications with a much longer timetable, is not regarded as helpful and has led to unnecessary discussion in the past should no longer be possible, at least not in such cases where a new MA is issued after the approval of the application. The CMDh regards the grouping of changes to the already approved strengths with an extension for a new strength or pharmaceutical form as not justified as the changes of type IA, IB and II will then be implemented much later in these already approved MAs which might lead to delayed introduction of safety relevant changes. Furthermore, it is anyway possible to include these necessary changes into an extension application resulting in a new MA as these can be part of the new MA application without having to declare them as a grouping.

It is therefore recommended to allow the grouping of variations and an extension application only in those cases where the extension application will be included in the existing licences but not when they are issued a new MA at the EoP.

Furthermore, the definitions of extension applications according to Annex I should be amended in order to introduce a different handling and timelines for extension applications resulting in a new strength/pharmaceutical forms and those being included in the already existing strengths/pharmaceutical forms.

### **11.1. Proposed solutions – in legislation**

Article 19, Annex III and Annex V in regulation no. 1234/2008 should be amended as follows:

Article 19

Extensions of marketing authorisations

1. An application for an extension of a marketing authorisation **according to Annex I** shall be evaluated in accordance with the same procedure as for the initial marketing authorisation to which it relates **when it results in a new strength/pharmaceutical form after a positive outcome of the procedure.**

2. An extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation **An application for an extension of a marketing authorisation according to Annex I that will be included in the basic marketing authorisation shall be handled as a type II variation with an extended timeframe of 90 days (see Annex V).**

Annex III should be amended as follows:

1. One of the variations in the group is an extension of the marketing authorisation **that is included in the existing MA. An extension application that results in a new MA should not be grouped with (a) variation(s) with other changes to the already approved strengths/pharmaceutical forms.**

Annex V has to be amended to include:

**Applications for extensions of applications according to Annex I that will be included in the basic marketing authorisation.**

### ***11.2. Proposed solutions – in guidance***

n/a

## **12. Article 10b applications more than once in the same MS**

The current wording in Art. 10b (medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes) and in the Annex I, Part II, section 5 (new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product) has led to different interpretations among MS. Even though the European Commission has given their view that the use of Article 10b should not be limited to the first time certain active substances are combined in an FDC and see no reasons to prevent subsequent applicants from performing trials on the same combination of active substances, due to national court cases not all MS have been able to follow this advice. This could be resolved by removing reference to “not hitherto used” and “not previously authorised as a fixed combination medicinal product” in legislation.

Moreover, we have noted difficulties with FDCs for substitution indications. In some cases, an FDC has recently been approved and is under data exclusivity. Instead of awaiting the outcome of the data exclusivity period and submit a generic application, some applicants instead submit their own Art 10b. application. As they only claim substitution indication (i.e., the combined use is already recognised in

the SmPCs of the individual active substances) no own (pre)clinical data is required, the dossier requirements are limited to a rationale for the FDC + bioequivalence data but no own (pre)clinical data is required according to guidelines. Upon approval, these products can later on be used as reference medicinal products for generics, so we will have generics demonstrating bioequivalence to a product that itself was based on BE studies with other products. However, we don't want to close the possibility for FDC for substitution indications completely. There may be situations where it would be useful for patients to have access to a FDC but the originator companies have not themselves developed such FDC. It could be discussed if FDCs without own substantial (pre)clinical data could be approved under a subcategory of Art. 10b, without being eligible to become reference medicinal products for generics. This approach is favoured by several MS, while some MS claim that this would not be consistent with line extensions of innovator products and WEU applications that today can be used as reference medicinal products, even though they are partly based on bioequivalence or bridging studies.

Another option that has been discussed previously is to allow a FDC claiming a substitution indication to apply via Art. 10(1) or Art 10(3) with the monocomponents as reference medicinal products. Due to a number of reasons this option is not further pursued:

- The implications of having more than one reference medicinal product needs to be carefully considered e.g. in terms of data exclusivity or generic substitution
- The product information would differ between the FDC and the reference products

### **12.1. Proposed solutions – in legislation**

To make it clear that Art. 10b can be used more than once for the same combination, the following changes in Directive 2001/83/EC are proposed:

Article 10b

In the case of medicinal products containing **a combination of** active substances, **which are previously used individually** in the composition of authorised medicinal products ~~but not hitherto used in combination for therapeutic purposes~~, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance.

Annex I, Part II

5. Fixed combination medicinal products

Applications based upon Article 10(1)(b) shall relate to new medicinal products made of at least two **known** active substances ~~not previously authorised as a fixed combination medicinal product~~.

It is also suggested to introduce a subparagraph in Art. 10b for FDC for substitution indication:

**For combination products intended to be used in patients adequately controlled with two or more active substances used in combination, the type and quantity of supplementary data to be provided must comply with the relevant criteria stated in relevant guidelines.**

This could be accompanied by a statement in legislation that products authorised under this subparagraph cannot be used as reference medicinal products for generic applications, if agreed.

## **12.2. Proposed solutions – in guidance**

No major change in guidance seems necessary as the CHMP [Guideline on clinical development of fixed combination medicinal products \(europa.eu\)](#) already details the data that should accompany an application for a FDC for substitution indication regardless of the legal basis.

## **13. European Annex IID for MRP/DCP MAs**

To facilitate the regulatory process in MRP/DCP it is proposed to align CAPs and NAPs (approved via MRP/DCP) with respect to “Annex IID Conditions”. Annex IID for CAPs reflects the CHMP opinion on conditions and specific obligations, if/as applicable, to be imposed on the marketing authorisation and as such is a part of QRD template for CAPs. Annex II for CAPs covers more aspects of centralised MA, but these are specific for CAPs and do not “fit” into national MAs, thus only “Annex IID” for NAPs is proposed (*The working term **Annex IID** is used in the following text, but the change in terminology is foreseen as the term Annex IID does not make sense when there are no annexes established for MRP/DCP products where the final MA is granted nationally according to the national legislations*).

Annex-IID Conditions are post-authorisation measures which, whilst not precluding the approval of a marketing authorisation or other post-authorisation procedures, are considered to be key to the benefit / risk balance of the product. As these conditions to the marketing authorisation are part of MA and are legally binding, any modification proposal by the MAH with regards to their description or due date has to be submitted as a variation application and also final results leading to the fulfilment of the Annex II condition has to be submitted as a variation application.

Annex-IID Conditions are dominantly related to Pharmacovigilance and are tightly linked to the approved safety concerns in the RMP.

In summary:

**Article 21a:** Conditions at the time of granting of a marketing authorisation

**Article 22:** Marketing authorisation under exceptional circumstances with annual reassessment

**Article 22a:** Conditions imposed post approval e.g. in a variation procedure, referrals, renewals

**Article 22c:** obligation to include information on conditions in risk management system (and summary) and to inform EMA.

The legislation requires that the conditions pursuant to Articles 21a, 22 or 22a of Directive 2001/83/EC are published together with the marketing authorisation.

Dir 2001/83/EC, Art 21.3:

*“The national competent authorities shall without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for the fulfillment of those conditions for each medicinal product which they have authorised.”*

Currently conditions in **MRP/DCP new applications** are included in the RMS Assessment Report (DCP AR Overview section VI.3 “List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC” or MRP AR section V.1 “Conditions for the marketing authorisation”) and DCP/MRP End of Procedure

notification section "Conditions to Marketing Authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC" and in the PAR, in **renewals** in the RMS Renewal Assessment Report (unless shortened renewal is followed) in section 1 and section 6 and in **variations** in PVAR/FVAR: I. Recommendation, if applicable.

**EU-standard annex IID (in accordance with annex IID for CAPs)** that includes agreed conditions for the safe and effective use of the medicinal product during the "European phase of the procedure" would not supersede individual national Marketing Authorisation decisions, but could be very valuable for documenting conditions and for traceability purposes throughout the whole product life-cycle. The NCAs will then be able to use this Annex IID and add it to the national marketing authorisation, as a separate document or include this in the marketing authorization, as applicable in the member state.

Annex 6 of RMP will always offer the possibility to tailor key elements or educational material itself to country specific situations which is not possible within a condition imposed to all MS concerned.

It is proposed that Annex IID for NAPs would be a separate EoP document generated after MRP/DCP, with a format aligned with Annex IID for CAPs.

**Annex II: CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**, i.e. narrowed down to annex IID only for CAPs, with conditions in bullet points + general RMP statement "*The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP*".

It is proposed to include **Annex IID in the dossier, i.e. in eCTD module 1.3** in order to keep track of the conditions, especially for the purpose of future variations amending/deleting conditions.

All products approved in the DCP and MRP are listed in the **MRI product Index**. For each product the SmPC, PL and PAR are already attached. The Annex IID conditions pursuant to Articles 21a, 22 or 22a for the marketing authorisation could be newly included as a separate document. If within a variation or renewal the conditions will be updated (condition deleted/amended/added) Annex IID should then be updated accordingly.

Also, in accordance with **Article 22c the member states shall inform the EMA** of the marketing authorisations that they have granted subject to conditions pursuant to Articles 21a, 22 or 22a. In MRP & DCP procedures it is expected that the RMS on behalf of the CMSs shall inform the EMA of the conditions agreed at the end of the procedure, but in practise this is not very often done. By publishing Annex IID in MRI products index this requirement would be covered as well.

### ***13.1. Proposed solutions – in legislation***

It is proposed to use the text of the Article 9.4 c) of the Regulation 726/2004 as a basis for Directive update with regard to MRP/DCP products and details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product to be annexed to the End of Procedure document.

Annex IID should only be applicable prospectively for **new MAAs** and in case of already **authorised products** only **when new condition** is imposed.

### **13.2. Proposed solutions – in guidance**

All CMDh Guidances would have to be updated, where relevant, if the Annex IID is established for MRP/DCP products.

## **14. Learning from the NVR**

We should adapt to some of the new contents that have been introduced via the new Veterinary Regulation. However, it should be regarded that not all of these changes seem suitable for the human medicinal products. Positive and negative aspects are described below.

### **a) Validation/Assessment step I: action on premature/incomplete dossiers**

In light of streamlining the procedures, the issue related to the need for defining the details of a fast track procedure to deliver early stage negative opinions has been raised, with a view to freeing up resources for more mature/promising applications.

Some generic dossiers submitted by Applicants via DC procedures have main deficiencies in the documentation to support the application based on the NtA/Guidelines requirements (e.g. lack of the Bioequivalence (BE) study in fed conditions as needed for a specific active substance, lack of the BE study in case the waiver is not applicable etc). However, based on *the 2001/83/EC*, the NCAs may, where appropriate, require the applicant to supplement the particulars accompanying the application although it lacks in main data, and the procedures should be started. It leads to work for assessors on a critically deficient application which would have a negative opinion.

The possibility to assess the main requirements of the NtA/guidelines during the validation phase could be taken into account to solve this issue, avoiding starting a procedure based on a dossier with serious deficiencies. It would optimize procedures and save time/resources which could be aimed to more appropriate dossiers instead. However, in case the proposed assessment during the validation step would be considered, the current guidance/templates and timeline should be broadly updated to add details on it.

Another possibility could be based on providing the preliminary assessment report during the step I leading to the conclusion with negative opinion during this step, without waiting for the full clock stop and the step II. This option would just partially solve the issue related to free up resources and time; however, it would provide a negative opinion based on a complete assessment, which could be more appropriate from a legal point of view. Moreover, the current guidance/ templates and timeline should be just slightly updated because the preliminary assessment during step I is already adopted; thus, just the mention of the early negative opinion should be added. See also concept paper no. 11.

Moreover, the RMS should inform the Applicant as a preliminary opinion, setting a very short timeline to try to send the lacking data or to take into account the withdrawal of the application.

### **b) Translation requirement**

It is often noted that applicants are not providing NCAs with the national translation after the end of a new application procedure. Some member states are issuing MAs based on the English texts but some have to wait – partly for years – for the submission of the translated Product Information. It is therefore recommended to take over the new rules from the NVR also to the human part where

applicable: If the applicant fails to provide a complete translation after the EoP within a period of six months the application shall be considered to be withdrawn in those member states that require the submission of national translations for issuing a MA.

This topic is also related to concept paper no. 12.

### **c) Re-examination for MAHs**

See proposal in topic 6 above.

### **d) Minimum of 12 months between NP and MRP**

It is increasingly noted that applicants are choosing the national marketing authorisation application followed by MRP in order to circumvent the use of DCP. In order to avoid the use of the MRP instead of the DCP it should be included in legislation that an MRP may only be started after a minimum of 12 months after the approval of a purely national marketing authorisation application and the issuing of the national MA. In the NVR this period is included with 6 months but from CMDh perspective this period is not long enough and should be extended to 12 months.

### **e) Subsequent recognition in MRP and DCP**

The NVR offers the opportunity for a kind of "silent adoption" for repeat use procedure when the product is already approved in several member states. This procedure seems to have no advantage over the currently used repeat use procedures for human medicinal products. The documentation to be provided by the RMS is identical and the timeline of 60 days procedures as well. For both, human and veterinary products the procedure will be referred to the CMD in case no agreement can be reached. The Repeat Use procedure for human medicinal products has several advantages over the veterinary procedure: the timetable is flexible and the procedure can even be agreed on as a 0-Day procedure when RMS and CMS agree on that without any necessary changes in legislation. In case of disagreement by the end due to PSRPH of a CMS a CMDh referral is foreseen so that all member states can give their point of view. It is therefore recommended not to change the current procedure and not to take over the procedure from the NVR to human medicinal products. See instead proposals under topic 4 above.

### **f) Review procedure**

See proposal in topic 7 above.

### **g) Union product database**

The system of a joint database seems to be a good option for easier handling of the procedures in the long-term. However, this database should be connected to national databases so that product specific data can be taken from one and only database. As long as not all details of a medicinal product can be included in such a database it is not regarded as sufficient to handle the approval and post-approval procedures for human medicinal products. It is essential for the handling of human medicinal products in the complete life-cycle that all aspects and the complete product history are available at the same database for each NCA. NPs as well as MRP/DCP have to be accessible in these national databases with their current maintenance status at any time. It is therefore strongly recommended to keep the

current system with the submission of eAF and eCTD sequence submissions via CESP until the SPOR system is well prepared for human medicinal products and can exchange information between SPOR and national databases. Having said that, once such an integrated system is in place, legislation should be flexible for allowing certain changes to be handled directly in this database.

#### **h) Delete renewals (at least for generics)**

Renewals have been deleted in the NVR. See topic 8 above. This is also handled in Concept Paper no. 13.

#### **i) Extensions with type II timetable**

Extensions as mentioned in subtopic 11 should be defined as a new application when resulting in a new MA after the EoP instead of as a variation and they should follow the timetable of new applications. Extensions that are included in the basic MA may be handled according to the extended type II timetable of 90 days as in the NVR. See also topic 11 above.

#### **j) Second clock stop in DCP**

A second clock stop in DCPs is not endorsed for human medicinal products due to the following reasons: DCPs are mainly used for generic applications acc. to Art. 10(1) of the legislation. These are procedures mainly clinically based on a bioequivalence study and a suitable quality dossier. These simplified applications work very well with a single clock stop as the applications are expected to be submitted in a high quality, a list of questions that is issued and addressed by the applicant in his response document. The introduction of a second clock stop could lead to a worsening of the quality of the submitted documents or the submission of premature dossiers as applicants have more time to submit responses. However, this will also lead to more assessment rounds by the assessors in NCAs and would use more resources than necessary. It is therefore strongly recommended to keep the DCP procedures with just one clock stop in order to improve the quality of the submitted dossiers.

#### **k) SmPC harmonisation process**

The CMDh creates a yearly list of products that are identified for the harmonisation of the SmPC via an Art. 30 referral procedure. However, it is increasingly difficult to prepare this list as the prerequisite for this exercise is that there is only one originator product approved in Europe. Very often, especially for very old products, there is no single originator so that these products cannot be included in Art. 30 procedures. But the disharmonisation of the SmPC of older products is a big problem for generic applications where each member state would like to adapt the generic to the originator licence on the local market. A harmonisation process for the originator or specific reference medicinal products could lead to an increase in harmonisation also for generics EU wide. A specific procedure for the harmonisation of generics would not be necessary as they have to adapt to the wording of the originator anyway. A harmonisation process led by CMDh would create less burden for the CHMP by Art. 30 referrals. A voting system with majority outcome should be implemented at CMDh level. This harmonisation process for RefMPs would extremely facilitate generic DCP applications and post-approval procedures.



## **14.1. Proposed solutions – in legislation**

### **a) Validation/Assessment step I: action on premature/incomplete dossiers:**

Use a similar wording as in the NVR:

Where the competent authority or the Agency, as applicable, considers that the application is incomplete, it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.

For closing a procedure after phase 1 with a negative outcome a similar wording should be included in the legislation – liaise with CP on the functioning of the centralised procedure (CP11).

### **b) Translation requirement**

Include in legislation in analogy to the NVR:

**If the applicant fails to provide a complete translation of the required documentation within a period of six months after having received the information referred to in Articles XXXX (dealing with end of procedures), the application shall be considered to have been withdrawn in those member states requiring national translations for issuing a MA.**

### **d) Minimum of 12 months between NP and MRP**

Include in legislation in the Articles on MRP in analogy to the NVR but increase the timeframe:

**A minimum of 12 months shall elapse between the decision granting the national marketing authorisation and the submission of the application for mutual recognition of that national marketing authorisation.**

### **k) SmPC harmonisation**

Implement the Article 70 from the NVR also for human medicinal products but not Art. 71 and especially not Art. 72. The project may not be limited to products authorised only after 10/2005, it is essential to make it available especially for older products.

## **14.2. Proposed solutions – in guidance**

n/a

## **15. Allow MS to raise MO/PSRPH on the (lack of) ERP data**

The possibility to refer to a European reference medicinal product (ERP) in applications made via Art. 10.1, 10.3 and 10.4 when the reference medicinal product (RefMP) is not/has not been authorised in

the MS where the application is made was introduced in 2005. Although we acknowledge that this increases availability of generic products in the EU, we have also encountered some difficulties with this concept. Even though a marketing authorisation should be based on the same EU requirements and principles in all MSs, there is a difference in the threshold to *keep* a product with an existing MA on the market and the threshold to *grant* a new marketing authorisation for said product. However, in an application made under Art. 10, MS can only raise major objections or potential serious risk to public health on elements included in the submitted dossier, and not on data related to the RefMP. In theory, the MS could instead request an Art. 30/31 referral for the RefMP/active substance, but this is difficult in practice as the data for the RefMP is not fully available to that MS. There have even been cases where the originator was refused in a MS, but generics have to be approved based on the ERP concept. We acknowledge the need to keep the possibility to apply the ERP concept in certain situations, but would like to discuss the possibility to introduce an opportunity for MS to raise major objections or potential serious risk to public health also on the (lack of) ERP data?

### **15.1. Proposed solutions – in legislation**

Different options could be looked into:

1. Remove the possibility to use ERP completely?

+ It would be straightforward to change in legislation

- Most MS probably have a need to accept ERP, at least in some cases, to get generics on their market

2. Could it be optional for MS to accept ERP?

+ Would be helpful if a MS could opt-out from a procedure if they don't accept the ERP in a particular application, while still letting the other MS concerned in the procedure accept it. Everybody gets what they want.

- Hardly feasible as it would lead to case by case MS/national decision in common EU legislation

3. Allow CMS to raise PSRPH on the (lack) of ERP data and trigger a CMDh referral?

+ In some cases maybe more data on the ERP could be provided by the ERP MS during the referral and a useful discussion could take place

- but in most cases there would be no data to discuss, and the generic will be approved as we can't question the ERP data within this referral

- Even if we would find a way to make it clear in legislation that PSRPH can be raised also on the ERP data and this would lead to an Art. 29 referral, how should the decision be taken? Most likely, MS who have/have had a version of the ERP authorised will vote positively, while MS who have earlier refused applications for the ERP or where the ERP is new and consider there is a lack of data will vote negatively. And it is difficult to see that CMDh/CHMP would be able to say that the RMS/CMS should not authorise a generic because the ERP data is missing/not up-to-date, especially not without taking any action on the ERP itself.

4. Automatic art. 31 referral to CHMP in case of PSRPH on ERP data raised in a generic application?

As none of the above options seems feasible, we remain in the current situation where an art. 30/31 to CHMP may be triggered for the ERP. But this has not worked in the past, as it has proved difficult for the objecting CMS to provide grounds for the referral to EMA. Maybe this could be facilitated by some rewording in legislation, either by amending art. 31 to add this specific situation or to add in art. 29 that in case a CMS has doubts on the ERP an art. 31 referral for the ERP will automatically be started. This could be accompanied by a statement that MS may await the outcome of the referral before concluding on the generic application, even though the generic application would not be directly involved in the referral. This would serve two purposes. Firstly, NCAs would not have to issue an MA

they are not in agreement with and that some months later may have to be changed. Secondly, if applicants know in advance that there will be a potential delay to the grant of the MA, they may be more careful when selecting the reference product and which indications to apply for.

### ***15.2. Proposed solutions – in guidance***

n/a

## **16. Clarify the use of MRP/DCP for traditional herbal medicinal products**

Currently there are different interpretations in relation to the use of MRP/DCP for the registration of THMPs that has been previously discussed within CMDh and HMPC:

- Is MRP/DCP mandatory for THMPs with a Community monograph or Community list entry, when intended for more than one MS, even though Art. 17.2 and Art. 18 does not apply to THMPs?
- Is MRP/DCP possible for THMPs even if neither a Community list entry nor a Community monograph exists?

CMDh has published Q&As confirming these statements but noting that it is up to the NCAs to decide. Legislation is therefore being applied differently across MS. To avoid this in the future, it would be preferable if the legislation could be clearer on this.

### ***16.1. Proposed solutions – in legislation***

It should be clearly stated in the legislation if MRP/DCP is mandatory for all THMPs, when intended for more than one MS, at least if a Community list entry or a Community monograph exists. For THMPs not included in a Community list entry or a Community monograph, MRP/DCP should be possible, but it needs to be further discussed if the procedural route is the choice of the applicant or the NCA.

### ***16.2. Proposed solutions – in guidance***

n/a

## **17. Include traditional herbal medicinal products and homeopathic medicinal products in the scope of the variation regulation?**

Currently there are national rules for variations for THMPs and homeopathic medicinal products, but CMDh has agreed in a Q&A to apply the variation regulation by analogy, in case MRP/DCP has been used for the registration of a THMP, in order to keep the dossier harmonised.

### ***17.1. Proposed solutions – in legislation***

It is proposed to extend the scope of the variation regulation to also include THMPs and homeopathic medicinal products, at least if they have been registered via MRP/DCP.

### ***17.2. Proposed solutions – in guidance***

n/a

## 02. Concept paper for EC on **Generics and Biosimilars**

**Main theme:** Simplification, need for new concepts, full readiness for copies of complex products like ATMPs, drug device combinations etc.

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Lead	<b>Experts from CMDh/EMA</b>
Drafting Group	Experts from CHMP, CAT, BWP, QWP, BMWP, PKWP and EMA

### ***Topic proposals from EC request***

- 1. Complex generics*
- 2. Adapted simpler system for generics*
- 3. New procedural elements (WP supporting CHMP assessment)*
- 4. Certification of certain elements to allow for multiple use and avoid duplication of assessment (bioequivalence studies - core SmPC)*
- 5. Drug device combinations as generics*
- 6. ATMPs as generics/biosimilars*
- 7. CHMP opinions on interchangeability*
- 8. Vaccines as generics/biosimilars*
- 9. Accepting use of non-EU reference products for bioequivalence studies beyond biosimilars (impact on use of EU reference products to be considered)*
- 10. Remove need to have the same name for all MS for generics of CAPs in MRP/DCP*
- 11. Concept of regulatory data protection - reference to vs actual submission of data*
- 12. Dedicated regulatory pathway for repurposing*

# Recommendations for change

## 1. Complex generics

There is no definition of complex generics in the EU legislation.

However, for some products with specialised dosage forms (e.g. liposomal products), peptides, polymeric compounds, FDC, product with a specified route of administration (e.g. locally applied and locally acting products such as ophthalmological products) or in particular modified release dosage forms (e.g. prolonged release dosage forms, delayed release dosage form, multiphasic release dosage forms, intramuscular/subcutaneous depot formulations, transdermal drug delivery systems) demonstration of pharmaceutical equivalence and bioequivalence may be difficult or not considered sufficient for the support of MAA. Consequently, these applications meet the criteria of Art. 10(1) – generic application and of Art. 10(3) – hybrid application.

No separate legal basis for complex generics is needed as they already fall within Art. 10(1) – generic application and Art. 10(3), but it is essential to concretely define complex generics in a specific guidance document.

Furthermore there is a Quality Q&A on EMA website for clarification of complex manufacturing processes complex manufacturing process is defined a process which includes one or more steps that may give rise to scale up difficulties, however, complex manufacturing process is defined to cover situations where the link between quality characteristics and in-vivo performance is not fully understood (e.g. nanomedicines).

So when establishing definitions of complex generics we should have in mind already existing EMA publications so that we stay consistent.

From a chemical quality point of view, a simplified registration is not really possible. Each generic dossier has to be evaluated on its own merit and needs full assessment.

On the other hand also some of the defined complex generics (liposomes, ophthalmic, modified release dosage forms...) are also authorised via DCP procedures, so mandatory centralised procedure is not seen necessary from chemical quality point.

Note when referring to 'complex' generics and the difficulty in using conventional bioequivalence studies on which to base authorisation, care must be taken to avoid mixing up truly complex physico-chemical structures, complicated pharmacokinetic profiles etc with issues around feasibility of conducting comparative bioavailability or PK studies e.g. if a large sample size is needed due to high inter- or intra-subject variability; size or resource constraints shouldn't be the main impediment.

### **1.1. Proposed solutions – in legislation**

No legislative changes are considered necessary at the present time in relation to definition of complex generics.

### **1.2. Proposed solutions – in guidance**

It is essential to concretely define complex generics in a specific guidance document.

The current EMA approach to specify requirements based on regular release of product-specific guidance to support complex generic drug development should be continued. Moreover, in case of

specific product development related questions, where case-by case analysis is necessary, Scientific Advice should be requested by the Applicant.

It is highly recommended that for the different types of generics (i.e. liposomes, iron colloids and complexes, polypeptides, APIs from natural sources, nanoproducts, macromolecules) specific guidance documents to be developed with the specific requirements. This could serve as support for both the developer and the assessors of such kind of products. These guidance could include requirements for physio-chemical comparability techniques (perhaps by using new analytical tools), necessary non-clinical and clinical studies, or as a replacement of in vivo studies specific, accurate, reproducible and sensitive in vitro tests or performance characterization requirements for integral medical devices). As in several cases the manufacturing process is inherently much more variable than for a simple generic product, solely the pharmaceutical and bioequivalence study is not enough proof for equivalence, but also other pharmacokinetic and pharmacodynamics studies may be needed. Generally, case by case analysis cannot be excluded.

With respect to modified release dosage forms, these can be generics and can be submitted as a 10(1) application. However, in case when due to the type of subjects used in the studies (for example, only patients) and/or the interval of administration (being too long), make that the usual required BE studies cannot be fully performed. Sometimes, single dose studies are not possible to be performed. Other times, multiple dose studies may be so time demanding that may be impracticable.

## **2. Adapted simpler system for generics**

Generics are a very important means to support availability of products on the European market. They can be submitted as simplified procedures acc. to Article 10 of Directive 2001/83. However, the experience shows that there is still room for improvement, either by changing the legislation to allow more flexibility or by facilitating procedures by digital tools. The most important issue is to avoid duplication of work which is covered in several subsections of this chapter.

### ***a) Simplification with regard to Module 3, quality dossier***

The authorization and post-approval monitoring of a "well-known substance" could be simplified from the clinical and pharmacovigilance point of view, as after 8 or more years of usage the knowledge is quite wide. However, from a quality point of view there is not much room for simplification. All generics have to have a full stand alone quality dossier and have to be assessed on their own merit and have the same requirements as the originator. For one drug substance there can be of course different ways of synthesis, so that a generic can have a quite different synthesis of the active substance compared to the originator product. Also for the manufacturing process full data have to be assessed. The assessment of the quality dossier can therefore not be reduced.

However, duplication of work in the National competent authorities (NCAs)s is created when identical dossiers are submitted by different applicants (who bought them) for marketing authorisation applications (MAAs) in different member states (MS) and with different reference member states(RMS). . For the assessment of the Active Substance Master File (ASMF) there is the ASMF worksharing but this is only on a voluntary basis, not sufficiently often used and still not working smoothly due to the fact that the lead assessor might change during the life cycle (an improvement of the procedure is discussed in Concept Paper 3). For such duplicate applications or identical drug product manufacturing sites for parallel submissions it would therefore be helpful, when also a process of assessment sharing could be created. It is currently already possible to re-use an assessment that is already uploaded in CTS for duplicate dossiers by other RMS, however, it is difficult to identify these duplicates early enough. Also, the applicants are often not aware that the same dossier is used by other applicants.

It would therefore be helpful if guidance could be prepared to share relevant dossier information in advance of submission (maybe already when applying for submission slots) in order to avoid unnecessary double work. In that respect, EMA is the logical partner to do this under a CMDh umbrella (i.e. CMDh is in the lead/has final responsibility); Exact roles would have to be defined/discussed. (see also proposal under f generic waves below)

### **2.a.1 Proposed solution – in legislation**

It would be helpful with a clear statement in legislation that member states may exchange any information about applications between MS and/or EMA, as some MS today have national law prohibiting them to share assessments automatically with EMA/MS not concerned by the application.

Also exchange of information with National Pharmacopoeia Authorities and/or EDQM is regarded as helpful.

It is expected that a single ASMF procedure will be addressed separately in concept paper topic 3 ASMF so will not be further addressed in this paper.

#### **b) Adequate use of well-established use application**

1) To legally enforce a current recommendation that well-established use application (under article 10a of Directive 2001/83/EC) should not be used as an alternative to other legal basis in particular generic (or hybrid) when a reference medicinal product exists.

This is currently recommended at two levels:

- by the European Commission in the Notice to Applicant, volume 2A, chapter 1 which states that *"The well-established medicinal use legal basis is to be used only in cases where all aspects of the safety and efficacy are demonstrated by reference to published scientific literature. It would derive that it should not be considered as an alternative to other legal basis such as Article 10 of Directive 2001/83/EC"*.
- by the CMDh in the Questions & Answer document on Applications for marketing authorisation, Q/A 10, which states that *"The CMDh recommends that applications in accordance with Article 10(a), Directive 2001/83/EC, be only submitted when there is no reference/medicinal product to which essential similarity can be claimed"*.

Member states have noticed that "generic products" are increasingly submitted via a well-established use application, either to circumvent data exclusivity of the reference medicinal product or submission acc. to Art. 8(3), or when the bioequivalence study failed to demonstrate the bioequivalence or to avoid the need to perform such bioequivalence study which is a condition for generic application.

Article 10a application is a derogation of a full application (according to article 8(3)) when it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

And, as stated by the Notice to applicant, *"the adequacy of the bibliographic evidence has to be assessed on a case by case basis in the understanding that applications under Article 10a **does not lower** the requirements of safety and efficacy that must be met"*.

Within the revision of the legislation, we suggest to legally enforce the recommendations and have a stricter framework of the article 10a application, so that well-established use application would not be



used anymore in case a reference medicinal product exists and generic or hybrid application is possible and to avoid cases of circumvention.

### 2) Biological products and well-established use

We suggest enforcing that well-established use is not a suitable legal basis for products containing biological active substance.

This is currently strongly recommended by CMDh in its questions & answers document on Biologicals, Q/A 3 : *"Given the complexity of the characterisation of the product, bibliographic applications according to Article 10a of Directive 2001/83/EC are strongly discouraged. It is highly recommended to ask the RMS for scientific and regulatory advice on the most appropriate legal basis"*.

Indeed, given the complexity of characterisation, it is not expected that the applicant will be able to demonstrate that the submitted literature is relevant for their product without additional studies.

Though there have been some examples in the past where the WEU application has been used, e.g. Albumin or allergens, the misuse for biologicals where the WEU application led to huge workload and negative outcome in the end is increasing, e.g. for heparins. A suitable way has to be found how to avoid these cases in order to save resources for both, member states and industry. A soft law, like CMDh guidance, is not considered sufficient to deal with these cases as applicants do not adhere to it.

However, it should be noted for this case that the definition of "biological medical product" is under discussion for revision in concept paper 5 so this outcome should be considered.

### 3) Well-established use to be restricted to the same route of administration

The well-established use applications are often used for products that have a different route of administration to that of the products described in literature. It is therefore very difficult to provide a suitable bridge between the product applied for and the available literature. It is therefore proposed to restrict the well established use applications to products that have not only the same active substance and indications but also the same route of administration.

## **2.b.1 Proposed solution – in legislation**

In order to ensure an adequate use of well-established use, it is proposed to state that well-established legal basis should not be an alternative to other legal basis and should be used only when there is no reference medicinal product to which essential similarity can be claimed (i.e. when generic / hybrid application is possible).

It is also suggested that article 10a should not be used for biological products. Two different solutions can be considered:

- 1) Exclude biological products from the scope of article 10a
  - + Clear legislation. Applicants will know this is not an option for biologicals. Easy to enforce for authorities (applications can be refused at validation)
  - Would not be possible to make any exemptions.
- 2) Include a restriction in Annex I

If the simple solution 1) cannot be shared it should at least be considered to include a restriction in Annex I in terms of which studies would be acceptable when establishing the similarity between the product applied for and the product(s) described in literature. It is

essential that the literature data covers the complete range of necessary studies and tests and that a bridge that **does not lower the requirements of safety and efficacy** is established from the literature used to the product applied for.

- + By limiting which studies can be accepted under article 10a, there would still be a possibility for suitable biologicals to apply via Article 10a
- Applicants may continue submitting also other biologicals under article 10a with a justification that no comparability data are needed for bridging. Will be difficult for authorities to refuse at validation, especially for old products in MRP.

Restrict the use of WEU to products with the same indication (i.e. to reflect the current restriction in the NtA Chapter I in the legislation). It should also be considered to further restrict to products with the same route of administration

According to Article 10a of Directive 2001/83/EC it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature if it can be demonstrated that the active substances of a medicinal product ***in the claimed therapeutic indication and with the same route of administration*** have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

### ***c) Generics to be submitted in NP/MRP/DCP only***

In order to use the expertise and resources most effectively in CHMP, it could be proposed to relieve the centralised procedure completely from Art. 10.1 generic applications. The vast majority of generic applications (also to centrally authorised reference medicinal products) apply via MRP/DCP, so we already have a well-functioning system with large experience, overseen by CMDh. This would allow CHMP to focus on the more complex applications, building on the existing expertise in the field of generics in MRP/DCP. It is acknowledged that some companies would like to use the CP to have their products approved immediately in all member states but this is also possible via the DCP. Authorising generics in CP does not seem to have improved availability in small markets, as reported during the pharma strategy workshops. Also, in order to streamline the work for assessment of duplicate dossiers of 10(1) applications (see section 2a) it would be advisable to keep all procedures concerned in one hand, i.e. the CMDh.

The above reflections do not represent a consolidated view in the network. An analysis of different models is provided in the concept paper on the scope of the centralised procedure.

### **2.c.1) Proposed solution – in legislation**

The proposal would mean that legislation should state that Art. 10.1 generics (also to centrally authorised reference medicinal products (CAP RefMP) should be authorised by the competent authorities of the Member States only, unless they fall within Art. 3.2s.(b) of Reg. 726/2004 (significant therapeutic, scientific or technical innovation Art. 10.3 hybrids and Art. 10.4 biosimilars can be more complex so could remain optional).

Probably the wording in Art. 3.3 of Reg. 726/2004 needs to be revised. Currently generics applied for in the centralised procedure refer to Art. 3.3, even though this article only mentions that these applications may be authorised by the NCAs under certain conditions, and only indirectly hinting that CP can also be used. Alternatively, the Annex "Medicinal Products to be authorised by the Community" could be supplemented with a section for "Medicinal Products to be authorised by the competent authorities of the Member States".

#### ***d) "Autogenerics" circumventing legislation***

The possibility to refer to a European reference medicinal product (ERP) in applications made via Art. 10.1, 10.3 and 10.4 when the reference medicinal product (RefMP) is/has not been authorised in the MS where the application is made was introduced in 2005. Although we acknowledge that this increases availability of generic products in the EU, we have also encountered some difficulties with this concept. Even though a marketing authorisation in one MS should be based on the same EU requirements and principles, there is a difference in the threshold to keep an existing MA on the market and the threshold for a new MS to grant a marketing authorisation for a product. When expanding an MA to more MS, a dossier that is up to date with current requirements is needed. However, in an application made under Art 10, new MS can only raise potential serious risk to public health on elements included in the submitted dossier, and not on data related to the RefMP. In theory, the new MS could request an Art 30/31 referral for the RefMP/active substance, but this is difficult in practice as the data for the RefMP is not fully available to the new MS. There have been cases where the originator of an old MA (which may even be a biological) in one MS wishes to either expand into other MS and/or submit an extension of their product. Instead of updating their dossier to current requirements followed by an MRP to new CMS, which would be the expected route, the applicant does not update the dossier but instead submits an Art. 10 application in new MS, making reference to their own product via the ERP concept ("autogeneric").

Furthermore, the autogeneric situation could also result in that a company registers an autogeneric and then does not market the RefMP anymore, so that there is no reference product available anymore and consequently no generics applications are possible.

#### **2.d.1 Proposed solution – in legislation**

To avoid this circumvention of the legislation, it is proposed to restrict access to Art. 10.1 and 10.4 so that "autogenerics" would have to apply via Art. 10c informed consent while an extension application should be submitted instead of Art. 10.3. As these procedures are limited to the member states with an existing MA, it would prevent further cases where a new MS doesn't have access to all data.

Furthermore, when the innovator company applies for an autogeneric in a member state where the reference medicinal product is not approved or marketed the innovator should submit the dossier of the reference medicinal product to those member states concerned so that they have all relevant information available in case they see a need for triggering an Art. 30/31 referral against the reference medicinal product or, resp., the active substance.

For those autogenerics that would still be allowed it should be made clear in legislation that they belong to the same global marketing authorisation as the RefMP so they can be used as reference medicinal products for generics in those cases where the innovator has withdrawn the RefMP after approval of the autogeneric.

One element that would need to be analysed is whether it is legally feasible to prevent an innovator from submitting an application under article 10.

It is noted that the problem above described is not applicable to the centralised procedure.

#### ***e )Applications with a biological reference product***

The legislation does not provide a clear basis for a number of situations involving a biological reference product.

-There is no clear regulation if the new product is a 'chemical' copy of a biological reference product . Either a separate legal basis, or a clear statement in the NtA which basis would be valid, would be helpful clarification. In addition, data requirements would need to be further defined.

- More flexibility with regard to the nature of data (i.e. quality and/or pre-clinical and/or clinical) is needed following the experience acquired with biosimilar applications and the evolution of the state-of-the-art.

Currently, duplicates of biological reference products can apply via Art. 10.1 as they do not meet the criteria of Art. 10.4. This should preferably be avoided in the future by a rewording of Art. 10(4); in conjunction with changes to the scope of 10(1) (see also above).

- possibility of differences vs. the biological RMP (concept of hybrid medicinal product applied to biological product) should be mentioned without creating confusion with the concept of 'biosimilar', i.e. a copy of a biological product. Avoiding this confusion is essential to not blur the message about confidence on biosimilar and downstream decision of interchangeability. It is therefore proposed to consider the creation of a separate legal basis by analogy to hybrid medicinal products under article 10(3) to regulate the differences vs. a biological RMP (e.g. new indication, pharmaceutical form, route of administration, strength).

### **2.e.1 Proposed solution – in legislation**

#### **Use of *lex specialis* legal basis for copy of biological medicinal products**

It is suggested to reword Art 10.4 to direct all applications referring to a biological reference product to Art 10.4.

This would exclude biologicals and/or chemical copies of biologicals from 10(1) and 10(3). Another option would be a clear statement in NtA which basis would be valid.

#### **Legal basis for products differing from the biological RMP**

In addition to the above points, it may be useful for legal certainty to explicit in the legislation the possibility for a medicinal product referring to a biological reference medicinal product to have differences with the latter, e.g. new indication, strength, pharmaceutical form, route of administration. Whilst changes could be introduced as a variation in the post-authorisation setting, there are cases where an applicant may conduct a new development (e.g. repurposing of a biological medicinal product) that would justify an approach similar to 'hybrid' for chemicals as of the initial MA (e.g. repurposing). In such case, a new legal basis could be introduced to reflect the possibility of an 'hybrid biological' that would consist of a reference to certain pre-clinical/clinical of a reference biological medicinal product (supported by an adequate bridge to the RMP to rely on the referred data), completed by new pre-clinical/clinical data to support the differences vs the RMP (e.g. a new indication).

The above reflections do not represent a consolidated view in the network.

### **f) Generics waves**

When an innovator medicinal product has no longer data protection, generic pharmaceutical companies throughout the world initiate to develop generic products of that innovator product. In Europe we notice that one generic product developed by a company is sold to many other companies and all these companies initiate one or many more DCP procedures in Europe with different combinations of RMS-

and CMS countries per application, and often also with copy application to follow for newly interested companies. There are many examples of so-called generic waves from the last fifteen years.

Currently such generic wave produces a multiplication of assessments by NCA authorities throughout Europe, producing assessment reports and comment reports all about the same Module 3 of the same medicinal product developed by one generic product dossier holder (GPDH) and to be produced on the same manufacturing site(s). The result of such 'generic wave' is that many national competent authorities are assessing the same Module 3.. So after the approval of these medicinal products the companies and the NCAs could have to deal with the maintenance and assessment of some slightly different versions of "the same" Module 3,, yet still concerning one and the same medicinal product that is manufactured.

The same situation happens in case of BE studies which are often identical in parallel procedures even if Module 3 is different

If a company has to introduce a change to the quality of the medicinal product, a variation application needs to be done for each DCP procedure of that medicinal product, that again has to be dealt with by all member states, and even for many member states also many times if the product has been approved in several different procedures with different applicants

### **2.f.1 Proposed solution – in guidance**

Improved utilization of CTS, e.g.: Changes in CTS can be introduced in that way that there are fields for ASMFs, drug product manufacturing sites and BE studies with the CRO study numbers etc. Project managers will complete this data in CTS. When the next application for the same active substance is submitted it would be ideal if the system would give a signal when same manufacturers or study numbers are used. If this is not automatically possible there should be an easy research function where this can be checked by the project management. Assessment reports for the first product could then be re-used for follow-up procedures of other applicants by different RMS.

More centralised trainings for quality assessors and adequate publication of harmonised decisions (Q&A on EMA homepage, Quality Database)

-Increase/improve use of work-sharing and certifications, if feasible mandatory. This could include certifications of whole module 3, not just ASMFs and CEPs. (see also subtopic 4 below).

-Mandatory reference to EU-SRS/SPOR databases if entries are available.

### ***g) definitions of generic and hybrid***

- **Allowing additional type of studies beyond bioQ for generics**

The current EU definition of generic and hybrid is unique in the World. Therefore, the generic concept of the EU is not understood outside the EU and it is not consistent with the scientific literature and other jurisdictions. In the EU a product that demonstrates equivalence by means of a pharmacodynamic or clinical endpoint has to be hybrid because its definition includes the cases where the bioequivalence cannot be demonstrated through bioavailability studies, but it is a generic in the rest of the world. This difference is based on the type of study used to demonstrate equivalence (pharmacokinetic vs. pharmacodynamic/clinical endpoints). However, reality is more complex than that simple dichotomy.

A locally acting product in principle needs therapeutic equivalence trials with a clinical or pharmacodynamic endpoint. Then, by definition it is hybrid in the EU, but if certain conditions are met it can be waived (e.g. solution for nebulization with the same excipients ) or an in vitro study may be enough for approval (e.g. suspension for nebulization) or even a pharmacokinetic bioequivalence study

can be suitable since the state of the art has changed in the last decades (e.g. pressurized metered dose inhaler measuring systemic absorption for safety and absorption from the lung to conclude on similar lung deposition). Similarly, a systemically acting drug requires a PK study, but if certain conditions are met it can be waived based on in vitro data. Therefore, the type of study that is expected in principle should not be the reason for the differentiation between generic and hybrid, because depending on certain conditions the expected study might not be submitted and a waiver requested.

Generic should be those products with the same active substance, strength and dosage form independently of the type of study employed to demonstrate equivalence ('generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose equivalence with the reference medicinal product has been demonstrated by appropriate studies) and hybrids should be those products where any of these characteristics differ, i.e. where the medicinal product does not fall within the definition of a generic medicinal product.

Appropriate guidelines should be drafted to clarify in which situations equivalence should be demonstrated by means of PD/Clinical endpoints or when PK studies are feasible and more sensitive.

The above would allow processing as generics products where equivalence can be demonstrated but not by the means of bioequivalence / PK comparative studies and where traditionally processed as hybrids (e.g. topical products, inhaled medicinal products....)

In summary, there is an agreement in the drafting group to delink the generic definition from the sole conduct of bioequivalence studies or justification of a biowaiver.

- **Approaches to define generics vs. hybrids**

Several approaches were expressed for policy considerations.

***Option 1: defining a generic with a restrictive interpretation of active substance and pharmaceutical form***

This approach would consider that any change to the active substance (e.g. different salts, esters, isomers, ethers, complexes, derivatives...) would be considered as a different active substance that should be processed under hybrids rather than generics.

In order to know if the different salts, esters, etc. differ significantly in properties with regard to safety and/or efficacy all products should submit pre-clinical and clinical data (or if obvious they would need to submit a justification or literature data that needs to be assessed by pre-clinical assessors or clinical assessors) to conclude based on that information if they are similar or differ significantly. It is illogical to decide in the validation if the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives differ significantly or not. This has to be decided during assessment. Currently any pre-clinical or clinical data submitted makes the product to be hybrid. In order to be consistent, these derivatives should be hybrids.

Different salts may exhibit different solubility – pH profile, which may affect the bioavailability in ways that cannot be assessed with the traditional bioequivalence studies in fasted state. For example, in healthy volunteers the different salt may be shown bioequivalent, but this might not be applicable to children or elderly patients with different pH in the gastrointestinal tract. Therefore, they should be considered hybrids and demonstration of bioequivalence should be more extensive, which may require the development of additional guidelines.

According to article 10.3 (*in case of changes in the active substance ..., vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided*), a change in active substance is considered as a hybrid application. However, it is not clear what type of change in active substance is referred to since the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance as generics, if they do not differ significantly in properties with regard to safety and/or efficacy.

As a matter of consequence the following sentence would need to be removed from the generic definition:

*"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy"*

In addition, the definition of pharmaceutical form should refer exclusively to the concept of EDQM standard terms and not considering that "The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form". This sentence should therefore be deleted from the generic definition.

The benefits of this narrow definition would be to foster international alignment of the definition of generics (i.e. US) and facilitate operational aspects. Indeed, it would allow operating a clear cut regarding the active substances that should be processed as generics versus the active substances processed as hybrid and to not presume that immediate-release oral pharmaceutical forms will not translate in significant differences in terms of efficacy and/or safety.

It would be essential to clarify in the corresponding guidelines if it is possible or not to demonstrate equivalence by means of PD/Clinical endpoints when PK studies are feasible and more sensitive. For example, if PK fails and a clinical study is used to show that the PK differences are not clinically relevant, the existing PK differences would make such product to be hybrid.

In the case of hybrids, it would be necessary to clarify that the pre-clinical or clinical studies should be conducted as needed to be consistent with the waiver possible for generics, which is described in the sentence "Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines". The same could be applied to hybrids since in some cases pre-clinical or clinical trials may not be needed.

### **Option 2: Differentiating generics and hybrid based on the aim of the application**

Currently hybrids include both products that differ from the reference medicinal products (e.g. change of indication, strength, pharmaceutical form or route of administration), as well as products that whilst claiming they are 'the same' than the reference medicinal product can not demonstrate it by the means of a bioequivalence study. This is the case for instance of topical or inhaled products.

As an extension of the approach to allow the reliance on other studies than bioequivalence studies for generics, a dichotomy between both applications could be to consider on whether the applied products is equivalent to the reference medicinal product or have different characteristics. It follows it could be considered:

- As generics all products having the same qualitative/quantitative compositions, the same (or less) indication(s), the same strength(s), the same pharmaceutical form(s), the same route of administration and claiming to be equivalent to the reference medicinal product (i.e. not differing significantly in terms of safety and/or efficacy)

- As hybrids medicinal products referring to certain non-clinical or clinical data but differing for instance in their indication, strength, pharmaceutical form or route of administration.

This approach would have the benefit to provide clarity in the concepts of generic (i.e. equivalent to the reference medicinal products) vs. hybrids (i.e. not equivalent to the reference medicinal product). This may also facilitate downstream national decisions affecting generics (such as substitution).

It is also proposed to maintain the current interpretation of 'same active substance' considering that different salts, esters, ethers, isomers, complexes or derivatives not differing significantly in terms of safety and/or efficacy, together with the burden on the proof for the applicant to demonstrate it: (art.10 2(b): *'The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant.'* As in most of the cases, a change in the active substance does not translate into significant clinical differences, this would still fulfil the concept of generics.

Similarly, it is proposed to maintain the current interpretation of the 'same pharmaceutical form', i.e. that *'the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form'*. As it is not expected that this change of immediate-release pharmaceutical forms does not affect the equivalence of the applied product vs. the reference medicinal product, this would still fulfil the concept of generics. Should the change of pharmaceutical form affect the equivalence, then the conditions of the generic would not be met and therefore the product not approvable. The sentence could however be considered to be reworded to make explicit that it should not affect the equivalence between the applied medicinal product and the reference medicinal product.

These interpretations of 'same active substance' and 'same pharmaceutical form' would capitalise on the case law, codified subsequently in the legislation, that define an extensive definition of generic for facilitate development, uptake and substitution of generic medicines. This case law was developed following strategies from innovators to develop minor changes to their products (e.g. change to the active substance or pharmaceutical form) to delay market access of generics at the time.

### **2.g.1 Proposed solution – in legislation**

To change the definition of generic medicinal product in article 10.2 (b):

*'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose equivalence with the reference medicinal product has been demonstrated by appropriate studies as defined in the appropriate detailed guidelines.*

Whilst there is consensus of the above definition of generic, there are different policy options as previously described on the concept of 'active substance' and 'pharmaceutical form' for the purpose of generic.

Whilst some members expressed that additional flexibility could be provided in corresponding guidelines could define what is considered the same active substance or the same dosage form, since these criteria may evolve according to the scientific knowledge. For example, if agreed, a solution for injection and a power and solvent for solution for injection could be considered the same dosage form since they are an identical solution at the time of administration. Certain types of salts that are highly



soluble could be considered the same, other members consider that the interpretation of this concept should be included in the legislation to allow legal certainty on the qualification of generics vs hybrids.

To change the definition of hybrid application in article 10.3:

*In cases where the medicinal product demonstrates equivalence or another suitable bridge to the reference medicinal product but does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or in case of changes in the posology, route of administration or therapeutic indications, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests and/or clinical trials shall be provided as needed to demonstrate equivalence or another suitable bridge to the reference product and any potential additional claim.*

Guidelines should be developed/amended accordingly to provide scientific support and predictability to the applicants in the data expected to be generated to support their generic/hybrid applications. The corresponding guidelines could define what studies are required depending on the type of differences and scenarios. For example, a solution in a single unit container (sachet) and a solution in a bottle might be waived even if hybrid due to the different strength.

The above proposals to amend the definitions of hybrid do not represent a consolidated view in the network. Alternatively, it could be considered to define generic as products relying on a reference medicinal product and having a similar efficacy and safety profile, whilst hybrid products would rely on a reference medicinal product but with differences in strength, a different indication, a different route of administration) – see option 2 above described.

#### ***i) Cross reference to hybrids***

As hybrids cannot be considered as reference medicinal products, they might be considered as protected forever since no-one can refer to them. To avoid this apparently infinite protection, it is possible to make reference to the hybrid in the cover letter and to conduct the bioequivalence studies versus the hybrid, but in the administrative form only one product is included, which has to be a complete dossier.

The legislation should state clearly that the evidence submitted by a different company to that of the reference medicinal product in a hybrid application (e.g. the evidence of therapeutic equivalence of the hybrid that is developed as prolonged release product where the immediate release product is the reference) does not deserve an exclusivity period and its clinical studies can be cross-referred when developing another abbreviated dossier.

Although it is obvious that the product used to define the exclusivity period / first authorised product in the EU, the product used as reference in each Member State (useful to identify the reference SmPC) and the product used in the BE study has to belong to the same marketing authorisation, this is not stated in the legislation and it could be clarified.

However, in the case where it is desired to develop a generic of a hybrid, this is not possible because it has to be submitted as a hybrid of the first product authorised in the EU with a complete dossier, even if the BE studies compare the new product with the previous hybrid.

In addition, the product used in the BE studies as reference is a hybrid that does not belong to the same global marketing authorisation of the first product authorised in the EU. Therefore, it is necessary to include this possibility in the legislation and that two different "reference" products can be cross-referred in the Administration Form.

Presently, it is necessary to include in the administrative data (eAF) the complete dossier as reference medicinal product (e.g. Immediate release product) and submit the different dosage form (e.g.

Prolonged release product) as hybrid due to the difference in dosage form. However, the labelling will be similar to that of the hybrid prolonged release product. This is announced in the cover letter. It could be solved if the administrative data accepted the cross-reference to two different products (the immediate release reference medicinal product and the prolonged release hybrid) although they belong to different global marketing authorisation in this exceptional case.

The above reflections do not represent a consolidated view in the network as it could be understood that there are still only one reference medicinal product (fulfilling the conditions of RMP, e.g. full dossier). The information from the hybrid could be seen as such not as a second RMP. If this approach is acceptable, then the discussions on GMA for the hybrid (part or not of the GMA of the RMP) becomes voided.

### **2.h.1 Proposed solution – in legislation**

To include a second paragraph in article 10.3:

Where reference is made to data provided in an application outside the global marketing authorization of the reference medicinal product and without data exclusivity, the applicant shall indicate in the application form the reference medicinal product for the purpose of data exclusivity and the medicinal product(s) to which equivalence has been demonstrated and a justification for making reference to a product outside of the global marketing authorisation. Otherwise, the reference medicinal product for data exclusivity and the medicinal product for the demonstration of equivalence shall belong to the same global marketing authorisation.

The above proposal does not represent a consolidated view in the network. It may also need to be further considered whether any proposals in respect of this issue are more suitable for guidance (e.g. NtA) or for legislation.

#### ***i) Difference between 8.3 mixed application and hybrid application.***

Hybrid applications according to article 10.3 and complete mixed applications according to article 8.3 should be better distinguished.

In those cases where the data provided by the applicant is basically the demonstration of therapeutic equivalence or another suitable bridge with a reference medical product, the application could be as hybrid even where additional clinical data is provided to support additional therapeutic indications or routes of administration.

If therapeutic equivalence or another suitable bridge with a reference medicinal product is not demonstrated formally, but only a certain degree of similarity is claimed vaguely to waive the requirement of the investigation of basic toxicological, pharmacokinetic and pharmacodynamic properties that are already well-known, the application should be submitted as complete mixed application since the efficacy and safety of the applied product is supported by data different from the demonstration of equivalence or another suitable bridge.

The above reflections do not represent a consolidated view in the network. . Choice of the legal basis is in the remit of the applicant as long as the requirements of the said legal basis are fulfilled. If further explanation on legal basis is needed, it should be considered whether any proposal would be more suitable for guidance (e.g. NtA) or legislation.

### **2i.1 Proposed solution – in legislation**

To define hybrid as indicated above.

*In cases where the medicinal product demonstrates equivalence or another suitable bridge to the reference medicinal product but does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or in case of changes in the posology, route of administration or therapeutic indications, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests and/or clinical trials shall be provided as needed to demonstrate equivalence or another suitable bridge to the reference product and any potential additional claim.*

The above proposal for definition for hybrid does not represent a consolidated view in the network. In a potential revision of the definition for hybrid (taking into also account point g in the document), it is recommended to clearly separate the notion of 'bridge' that allow reliance on the referred pre-clinical and/or clinical studies of the reference medicinal product and the additional pre-clinical and/or clinical data to supports the difference(s) vs. the RMP (e.g. new indication, pharmaceutical form, strength, route of administration).

### **3. New procedural elements (WP supporting CHMP assessment)**

#### *Generics*

With regard to the EC request to consider a dedicated working party to support CHMP in relation to generic applications, this is not supported in the context of other proposed initiatives (including those in Section 2).

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#### *Biosimilars*

For biological medicinal products submitted via the centralised procedure, including biosimilars, the CHMP already receives extensive support from the Biologics Working Party (BWP) in relation to quality aspects. This long standing arrangement works very well and is ensuring optimal use of the available expertise, meaning that quality matters are mainly discussed at BWP (which holds specific expertise in this area), leaving CHMP to focus mainly on (non-)clinical matters.

To further facilitate the work of CHMP, it could be an option to make further use of the expertise of the Biosimilar Medicinal Products Working Party (BMWP). This group holds specific expertise in the area of biosimilars (covering quality, non-clinical and clinical aspects) and would be well placed to provide input on (non-)clinical aspects as well as multidisciplinary matters, thus providing a link to the quality aspects addressed by BWP. This group is currently only providing input to initial Marketing Authorisation Applications on specific request from CHMP. If BWMP could be invited routinely to provide input on these procedures, it would allow CHMP to have better informed/more efficient discussions.

#### **1.1. Proposed solutions – in legislation**

No changes are considered necessary.

#### **1.2. Proposed solutions – in guidance**

The most effective way to improve scientific support to CHMP, if considered necessary, would be to strengthen the contribution of the existing working parties. This can be managed through internal

procedures and it should be noted that a review of the working parties organisation is currently ongoing.

## **4. Certification of certain elements to allow for multiple use and avoid duplication of assessment (bioequivalence studies – core SmPC)**

A generic/hybrid medicinal product can be evaluated under a centralized procedure or via the national or Mutual Recognition (MRP) or Decentralised (DCP) procedure, and the same product can be submitted multiple times in different routes of evaluation. In addition to these different lines of submission, it is also very frequent that several applications, by being copies of one another, share many common elements for assessment, including the same supporting bioequivalence (BE) study. This may result in duplication of assessment, with time losses and the risk of different outcomes in the network.

In addition, although in theory the Core parts of the SmPC should be the same as based on the same reference (originator) product, over time, however, with the various approval routes, differences may appear in SmPCs at national and Member State level and hence an Article 30 harmonisation referral procedure may be needed. In addition, there are still a lot of old SmPCs for reference products that have been approved nationally in the past in single Member States and are not harmonised and may even have different indications, age group, contraindications etc. They are sometimes not eligible for Art. 30 procedures as there are several other originators. The CMDh has published core SmPCs which work quite well and which can be adapted by type IB variations. Furthermore, the CMDh has promoted the variation worksharing for harmonisation of the SmPCs of purely national products, which is increasingly used, and works well, like a normal type II variation.

Many negative opinions or requests for referrals under Art 29 at CMDh are related to deficiencies in the BE studies reported in the DCP generic applications or to divergent opinions among MSs on these studies (please note that generic applications represent most of the DCP ones); thus a harmonised opinion on the BE studies is necessary.

### **4.1 Proposed solutions – in legislation**

Similar to the 'Qualification of novel methodologies for medicine development' (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0>), a new type of procedure resulting in an assessment certificate that could be used for later submission to other national/Mutual Recognition/Decentralized procedures could be created. This certificate could be obtained either prior to or after a centralised/decentralised procedure itself and should have a time-limited validity due to state-of-the art/ guidance changes.

Another option could be adopting a Bioequivalence Worksharing procedure (in line with the ASMF Worksharing procedure) to involve more Member States in the assessment of the BE study during the ongoing procedures to prepare an Assessment Report which could be adopted also in future applications (both CAPs and NAPs). Details on the WS procedure should be set and maybe a Working Group on this issue could be considered too.

A common repository or centralised database would need to be created to store the relevant certificates; otherwise a European Repository to collect the Assessment Reports from the BE WS could be set-up.

## **4.2 Proposed solutions – in guidance**

An EU Regulatory network-available master file on a product for PK, similar to the PKWP background monograph (Part A) of the product specific bioequivalence guidelines (PSBGLs) that underpin the publicly available (Part B) requirements for BE studies could be created. This file could be built up and maintained over the life-cycle of a product to 'certify' what is known about common elements (e.g. BCS, food, study design, NTI) for that product. Legislation might also be needed in addition to guidance to establish the 'PK file' concept and the roles and responsibilities for compiling and sharing the information.

Otherwise a "common" assessment report on the same BE studies to be adopted in different procedures could be taken into account too, based on a Worksharing procedure.

Regarding SmPC harmonization, this should be increased for old SmPCs. The CMDh therefore proposed in the concept paper on MRP/DCP to make the worksharing for such products mandatory, as it is foreseen in the NVR. And also the SmPC harmonisation proposal above under subtopic 2 is taken over from the NVR and could be an option for easier SmPC harmonisation processes than via Art. 30 procedure.

## **5. Drug device combinations as generics**

### *Analysis*

General issues relating to MDR implementation are considered to be outside the scope of this document.

Requirements to support the use of a medical device in apply to all medicines regardless of their legal basis. Based on the experience so far specifically for biosimilars and generics as DDC, no urgent issues have yet been encountered that would warrant any change in the legislation.

It is noted that some specific issues with regard to switching/interchangeability may exist for DDCs (e.g. switching from a DDC product to a generic DDC-product with a different device may not be straightforward, in particular in the context of automatic substitution). This point could be reflected upon further and guidance could be considered if the need arises.

### **5.1. Proposed solutions – in legislation**

No changes proposed.

### **5.2. Proposed solutions – in guidance**

Although more regulatory experience should be collected (particularly in view of the recent MDR implementation), guidance could be foreseen in relation to e.g. (a) regulatory requirements when developing biosimilar/generic products with different medical devices and (b) requirements ensuring safe switching as necessary for (automatic) substitution of generic/biosimilar products where different devices are used, particularly in case of complex devices.

## **6. ATMPs as generics/biosimilars**

### *Analysis*

ATMPs cover a wide range of complexity, from less complex products such as plasmids to very complex cell/tissue based products which are difficult to characterise and compare. Whereas it is currently difficult to foresee the possibility of biosimilars to more complex ATMPs, with advances in analytical and manufacturing technology it is expected that it will be technically possible to develop biosimilars of at least some types of ATMPs in the future. The current legislation and the guideline on similar biological medicinal products (CHMP/437/04 Rev 1) are phrased in such a way that does not per se exclude biosimilars of ATMPs. It is proposed to maintain the current flexibility which in principle allows biosimilar applications for all biologicals, without excluding certain product types/classes. From this point of view, no amendment to the legislation is considered necessary to allow biosimilars of ATMPs in the future. With respect to guidance it is noted that no MAAs or scientific advice requests for biosimilar ATMPs have been received by EMA. Hence the need to develop guidance in this area does not appear to be urgent.

From a regulatory viewpoint, it should be noted that there is an interdependency between the concepts of biosimilarity, orphan similarity and NAS. As delineations have to be evaluated scientifically and to be open for future developments it is proposed that detailed policy relating to these concepts is maintained as scientific guidance rather than being included in the legislation

### **6.1. Proposed solutions – in legislation**

The current legislation is considered adequate to cover the possibility of future ATMP biosimilars. Therefore, no changes are proposed.

### **6.2. Proposed solutions – in guidance**

The scientific principles outlined in the current biosimilar guidelines are considered applicable also to ATMPs. Specific guidance on biosimilars of ATMPs can be developed as and when the need arises (e.g. as an Annex to existing biosimilar guidelines as it has been done for specific products or product types such as monoclonal antibodies). Guidance would allow the necessary flexibility depending on the complexity of the product.

At this time no MAAs or scientific advice requests have been received, so the need for guidance does not appear to be urgent. Development of guidance should therefore wait until stakeholders indicate that biosimilar ATMPs are indeed being developed, so that guidance can take into account the state of the art.

## **7. CHMP opinions on interchangeability of biosimilars**

Interchangeability in the context of this concept paper means the prescriber-initiated exchange of one medicine for another with the same therapeutic intent. It does not refer to automatic substitution at the pharmacy level since this decision is taken by individual member states.

There is a current understanding that scientific issues will be addressed by EMA at a centralised level and economic decisions will always be taken at national level. However, interchangeability is a good example of a scientific issue that has economic ramifications and has therefore not being tackled centrally.

### **Rationale for change**

Physicians are often unclear about whether they can switch their patients from a reference biological medicinal product to a respective biosimilar or *vice versa*. The “similar-but-not-identical” paradigm

adds to this uncertainty and is also the argumentative basis for different recommendations on interchangeability expressed e.g. in the published literature or at congresses, but these recommendations are often influenced by stakeholder interests. Recommendations of the national authorities on interchangeability may also differ or are simply non-existent. These factors likely contribute to the slow uptake observed for (some) biosimilars in some countries.

So far, CHMP/EMA have been silent on this topic. However, CHMP has been assessing biosimilars for 15 years and has gained very profound understanding of biosimilar candidates from numerous substance classes. Considering that more than one hundred biosimilar submissions have been reviewed over the years, CHMP supports the scientific conclusion that products approved as biosimilars in the EU are interchangeable. A clear confirmation of this scientific position as part of the legislation or in guidance (see options below) is expected to provide valuable information and reassurance for downstream decision-making by prescribers, NCAs and HTAs. This scientific position is needed to provide a harmonized EU position that will reduce uncertainty at the scientific level and still leave any economic decision to be taken at national or regional level.

It is not considered necessary to perform an individual assessment on interchangeability at product level. Additional data, beyond what is currently required for demonstration of biosimilarity, is also not considered necessary as it would increase the burden both on biosimilar developers and the regulatory network, without added value from a scientific viewpoint.

### ***Proposed solutions – in legislation***

Two options were considered, option 2 is presented in case option 1 (preferred by the majority) is considered not appropriate or sufficient to achieve the goal of harmonisation:

1. No change in legislation necessary, a general statement on interchangeability could be envisaged in the form of a scientific position in biosimilar guidance (see section below).
2. Amending legislation to include, in a recital or article, a statement on the interchangeability of biosimilars with their reference medicinal product. For consistency, the same recital/article could also make reference on the interchangeability of generics. If necessary, the CHMP could further develop/reinforce on this position statement with a scientific opinion, updated guidance (as proposed below) or Q&A, as appropriate.

### ***Proposed solutions – in guidance***

As stated above, it is not considered necessary to establish additional data requirements to support a general position that biosimilars are considered interchangeable.

Existing biosimilar guidance would need to be updated to reflect the general position on interchangeability. The sentence "Evaluation of biosimilar medicines for authorisation purposes by the EMA does not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within the remit of the EU member states" in the *Guideline on similar biological medicinal products* (CHMP/437/04 Rev 1) would need to be modified.

In addition, CHMP could consider whether any amendments to the information included in the SmPC, EPAR or guidance for healthcare professionals would be necessary.

## **8. Vaccines as generics/biosimilars**

*Analysis*

The current legislation and the guideline on similar biological medicinal products (CHMP/437/04 Rev 1) are phrased in such a way that does not exclude biosimilars of vaccines. From this point of view, no amendment to the legislation is considered necessary to allow biosimilars of vaccines in the future. With regard to guidance, it is observed that there does not appear to be an urgent need, as only one scientific advice request and no Marketing Authorisation Applications for biosimilar vaccines have been received by EMA. Development of guidance is therefore not considered a priority.

### **8.1. Proposed solutions – in legislation**

The legislation is currently considered adequate to cover the possibility of future vaccine biosimilars. Therefore, no changes are proposed.

### **8.2. Proposed solutions – in guidance**

Specific guidance on biosimilars of vaccines can be developed if the need arises (e.g. as an Annex to existing biosimilar guidelines as it has been done for specific products or product types such as monoclonal antibodies). Guidance would allow the necessary flexibility depending on the complexity of the product, e.g. a simple recombinant protein vaccine could follow the same approach as already covered by existing guidance whereas e.g. attenuated/inactivated virus vaccines are more complex entities where specific guidance may be needed.

It is also observed that guidance might be useful to address comparability of adjuvants and (from a clinical point of view) appropriate correlates of protection if a comparative clinical study is foreseen.

However, at this time no Marketing Authorisation Applications have been received, and the interest has been very limited at the level of scientific advice, so the need for guidance does not appear to be urgent. Development of guidance should therefore wait until stakeholders indicate that biosimilar vaccines are indeed being developed, so that guidance can take into account the state of the art.

## **9. Accepting use of non-EU reference products beyond biosimilars (impact on use of EU reference products to be considered)**

The reference medicinal product for a generic or a hybrid application in the European Union is a medicinal product which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC and to which the application for marketing authorisation for a generic/hybrid medicinal product refers, by demonstration of equivalence.

Among other requirements, Applicants have to identify in the application form for the generic/hybrid medicinal product the medicinal product purchased from a member state of the European Union (product name, strength, pharmaceutical form, MAH, first authorisation, Member State) used for the bioequivalence study(ies) i.e. the EU reference product.

For generic/hybrid applications, no indirect comparison (demonstration of bioequivalence between EU and non-EU products) is an acceptable justification for using a bioequivalence study with a non-EU reference product as a surrogate for a bioequivalence study with an EU reference.

For hybrid applications, although an EU reference product must be used in the relevant bioequivalence (comparative bioavailability) study or therapeutic equivalence, data from studies with non-EU comparator products have been (rarely) used as supportive, e.g. for Cuprior *'a second PK study*



*performed to meet US registration requirements was submitted in form of a summary. Since conducted versus the US FDA approved product the data are only supportive, but informative for the characterisation of the PK behaviour (linear PK)'*

*([https://www.ema.europa.eu/en/documents/assessment-report/cuprior-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/cuprior-epar-public-assessment-report_en.pdf)).*

For biosimilars, the reference medicinal product must also be a medicinal product authorised in the EU, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in in vivo non-clinical studies (where needed) with a non-EU authorised comparator. In this case, it is the Applicant's responsibility to demonstrate that the comparator authorised outside the EU in countries with stringent regulatory requirements is representative of the reference product authorised in the EU.

Following the same rationale, it may well be the case that a non-EU comparator product may be used in the bioequivalence studies to support generic/hybrid applications. There are, however, a number of considerations, as follows:

- a) As a starting point, the EU reference and non-EU comparator products should be the 'same' i.e. same MAH, same composition, manufacture or 'sufficiently similar' to ensure interchangeability. This raises the question as to how this might be defined or how any differences might be handled.
- b) As for biosimilars, it should always be the applicant's responsibility to demonstrate that the comparator is representative of the reference product in the EU. However, experience and requirements for this are currently lacking for generics as to-date the approach has not been allowed and thus far any efforts have been on the level of broad statements or declarations from an applicant on similarity of composition, manufacture etc.
- c) Therefore, in order to assure the "regulatory" comparability, ideally it would be needed to have access to the data-file of the comparator in the non-EU country and not only the original submission but also all other changes in life cycle including variations to e.g. change excipients or manufacture, to account for possible changes in formulation over time.

It should be noted that in the EU network, there is already a simplified approach to generics/hybrids and the use of a non-EU comparator taking account of the above points would make the process far more complex for no obvious scientific gain. There may, however, be merit in a two-tiered approach e.g. for generic products the requirement for an EU reference product would remain unchanged as is, but for some particularly 'complex generics' (or 'hybrids' under the current legal basis) that requires studies beyond a bioQ/comparative PK studies that, where the required studies may be particularly complicated designs or difficult to reproduce, a non-EU comparator may perhaps be used in a specific context for comparative non-pharmacokinetic clinical studies. The requirement of an EU Reference medicinal product should, however, still remain and the Applicants would still have to demonstrate and prove the bridge or link between non-EU comparator and EU RMP (by analogy to the biosimilar approach) and only limited scenarios are foreseen where this approach might be applied

## **9.1 Proposed solutions – in legislation**

N/A

## **9.2 Proposed solutions – in guidance**

It is proposed that the global development approach for hybrid products (defined as per current legal basis) is considered where the establishment of appropriate comparability to the EU/EEA RMP requires conducting studies beyond bioequivalence/ comparative PK study. It is proposed that this approach could in some situations allow for use of a non-EU comparator for these types of studies, provided that bioequivalence/comparative PK studies would still be conducted with an EU/EEA RMP.

This approach should not be, however, used e.g. to overcome negative results in BE studies made with an EU reference product or in situations where bioequivalence can be demonstrated in the usual manner for generics.

The conditions for benefiting of this approach are summarised below:

- bioequivalence/comparative PK studies would be conducted with an EU/EEA RMP;
- to accept results of additional non-clinical and/or clinical studies with a non-EU/EEA sourced product;
- to require adequate data or information scientifically justifying the relevance of comparative data and establish an acceptable bridge to the EU/EEA-authorized RMP; Guidance would be needed on how 'sufficiently similar' or 'sameness' might be assessed between the comparator and the EU reference product.
- to only consider the non-EU/EEA authorised version of the RMP that has been authorised by a regulatory authority with similar scientific and regulatory standards as EMA or EEA competent authorities.

## **10. Remove need to have the same name for all MS for generics of CAPs in MRP/DCP**

This topic will be dealt with in concept paper 12 on product information

## **11. Concept of regulatory data protection – reference to vs actual submission of data**

Article 10(1) of Directive 2001/83/EC provides that "*By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, **the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials** if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community"* (emphasis added).

In turn, Article 14(11) of Regulation (EC) No 726/2004 states that: "*Without prejudice to the law on the protection of industrial and commercial property, **medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more***

*new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies” (emphasis added).*

Whilst it is clear that the above provisions allow for regulatory data protection (RDP) when a product is referenced in the context of an application for marketing authorisation submitted under Article 10 of Directive 2001/83/EC, it appears to be less clear whether said provisions also allow for RDP where the same pre-clinical tests and clinical trials are submitted in the context of an application under, for example, Article 8(3), Article 10a or Article 10b of Directive 2001/83/EC (e.g. scientific literature).

Guidance in this regard is found in Volume 2A of Chapter 1 of Notice to Applicants (NtA), where in Section 6.1.6 “Reliance on pre-clinical and clinical data contained in the dossier of a reference medicinal product under data exclusivity” it is stated that:

*“During the period of data exclusivity of a medicinal product, the data contained in the pre-clinical and clinical file of that product and obtained through access to documents or freedom of information legislation within the EU or in third countries, cannot be relied on by other applicants or the authorities in a subsequent application to ascertain the safety and efficacy of other products. As long as a product authorised in the EU is under data exclusivity, the reliance on published or unpublished pre-clinical and clinical data contained in the dossier of that product within the EU or in third countries by the competent authorities to grant a marketing authorisation would lead to a circumvention of the data exclusivity rules. Therefore, such application cannot be accepted”.*

It bears noting that currently, by way of submitting the form in application for marketing authorisation, applicants declare.

### **1.3. Proposed solutions – in legislation**

In order to rely on the enforceability power of a legal provision in cases where regulatory action is needed, it is suggested that the reach of RDP is explicitly included in legislation. The principles reflected in the wording above from Notice to Applicants could inspire the revision of Article 10 of the directive.

In this regard, and beyond considerations under Article 10 and RDP, it is recommended that a gap analysis is performed on the instances where regulatory guidance in Notice to Applicants is not explicitly provided in legislation, as it can be argued for the case presented above. Where justified for reasons of legal certainty, it could be considered to include in legislation those identified instances.

### **1.4. Proposed solutions – in guidance**

To complement the above proposed solution in legislation, NtA could be revised to further clarify whether a study performed to an one component medicinal product (A) authorised for over 8 years continues to be protected in case it is subsequently used in a fixed dose combination medicinal product (A+B) enjoying from data protection.

## **2. Dedicated regulatory pathway for repurposing**

The drafting group has been mandated to reflect whether an independent regulatory procedure dedicated to the repurposing would be of added value.

The drafting group of this concept paper considers that the current regulatory framework is adapted to the processing of repurposed applications, both in the context of MAA and variations.

It is noted that an important aspect is the interactions and cooperation between different stakeholders (e.g. academia, pharmaceutical industry...) – dedicated platform of interactions or specific scientific support (e.g. SA) could be considered for leveraging.

An important element is the lack of incentives for such development from the MAHs. Incentives in terms of data protection and/or reimbursement should be considered, acknowledging that such incentives should be proportionate to the improvement.

Despite incentives it might not be sufficient to stimulate the uptake by a business company (originator or generics/biosimilars) to apply for the new indication. Enhanced legal provisions to mandate or enforce MAHs to keep their product information up-to-date with newly available evidence even when not generated by them as MAH could be considered. Related questions of liability and obligations (e.g. pharmacovigilance, dedicated strength/formulation...) should be taken into account.

It might also be useful to analyse the challenges for applicants interested in repurposing to meet the required regulatory requirements for a marketing authorisation. For instance, it should be considered whether the paediatric requirements laid down in Regulation (EC) No 1901/2006 are adapted to the different situations of drug repurposing.

In addition, it could be explored whether it would have some benefits to have a mechanism for regulators to perform assessment of data generated by academia/not-for profit organisations when relevant to support PI update.

Finally, whilst the group fully supports promotion of any mechanism that would support clinical development and regulatory process to remedy off-label use or foster development of new therapeutic use, it is important to not downgrade standards for scientific evidence.

Any mechanism that would be considered to promote repurposing should take the above into consideration to avoid relaxation of scientific standards or disproportionate amount of resources needed from the regulators.

### 03. Concept paper for EC on **ASMF**

**Main theme:** Sketching out main elements and business processes that would be needed for a "single" certification procedure, including updates and any accompanying processes e.g. to monitor, inspect etc.

#### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of 'concept papers' on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts' reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic leads	Experts from CMDh/EMA
Drafting Group	Experts from CHMP, CAT, BWP, QWP, HMA, EDQM and EMA

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## Timelines

Kick-off meeting	15 October 2021
First drafting meeting	29 October 2021
Introductory briefing to CMDh, BWP, CAT	November
Second drafting meeting	17 November 2021
First consultation with QWP, IWG	November
First consultation with BWP, CAT, CMDh	December
Third drafting meeting	19 January 2022
Fourth drafting meeting	20 January 2022
Fifth drafting meeting	24 January 2022
Sixth drafting meeting	27 January 2022
Mature draft interim paper to be sent to EC + Committees / Working Parties	31 January 2022
Comments by EC, Committees / Working Parties	25 February 2022
Seventh drafting meeting	11 March 2022
Eighth drafting meeting	28 March 2022
Ninth drafting meeting	31 March 2022
Final paper transmission to EC	31 March 2022
Discussions on outstanding issues at Committees / Working Party level in case of comments on final paper received	April



## List of abbreviations

ADC	Antibody-drug conjugate
API	Active pharmaceutical ingredient (active substance)
AR	Assessment report
AS	Active substance
ASMF	Active substance master file
BWP	Biologics Working Party
CCI	Commercially confidential information
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised procedures
CMDv	Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary
CMS	Concerned Member State
CP	Centralised procedure
CTD	Common Technical Document
CTS	Communication and Tracking System
CVMP	Committee for Medicinal Products for Veterinary Use
DCP (DC)	Decentralised procedure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IT	Information technology
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MA	Marketing authorisation
MAA	Marketing Authorisation Application / Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
MAV	Marketing Authorisation Variation
MRP (MR)	Mutual recognition procedure
MS	Member State
NCA	National Competent Authority
OMCL	Official medicines control laboratories
Ph. Eur.	European Pharmacopoeia
PRAC	Pharmacovigilance Risk Assessment Committee
PSUSA	Periodic safety update report single assessment
Q&A	Questions and Answers
QC	Quality control
QP	Qualified Person
QWP	Quality Working Party
RMS	Reference Member State
VAMF	Vaccine Antigen Master File
WS	Worksharing

## Executive summary

Recommendations for change are centred around three main topics.

### 1. Single ASMF procedure including which competent authority to carry out the assessment, links with inspections

Main proposal focuses on a suggestion to suppress the link between the ASMF assessment and the MAA assessment by allowing the ASMF to be assessed as a stand-alone dossier.

Furthermore, it is suggested to establish a mandatory centralised/centrally coordinated procedure for assessment, which could be carried out via one of the following proposed approaches:

- CEP-like procedure: administration / coordination (of assessment and inspections) to be performed by a central entity (EDQM);
- Centralised – rapporteur procedure: administration / coordination (of assessment and inspections) to be performed by the EMA.

### 2. Extending scope and application of Master File concept to some raw and starting materials, some excipients, biologics, etc.

Two alternative proposals are suggested:

- To amend the legislation with the concept of master files in general and leave it to EMA / EC to manage the type of master file + scope of open and closed parts via a guideline in order to future-proof the legislation and allow flexibility in expanding the concept when a business case arises;
- To define extended master files in legislation as per below.

	Recommended inclusion	Not recommended inclusion	Further discussion could be needed
starting materials (viral vectors, cell lines and cell seeds, plasmids)			x
starting materials (chemicals)		x	
(critical) raw materials (media components, enzymes or growth factors)			x
raw materials (other than starting materials – for chemicals)		x	
API intermediates (when intermediate is chemical active substances by itself or used in conjugation of biologics)	x		
API intermediates of chemical active substances		x	

biologicals		x	
finished product intermediates		x	
excipients (or mixtures such as printing inks, co-processed excipients)		x	
flavouring			x
novel excipients	x		
adjuvants	x		
packaging		x	
analytical methods		x	
radiopharmaceutical precursors	x		

### 3. Interplay with CEP: Explore making CEP mandatory for pharmacopoeia substances

Three different viewpoints have been communicated by different Member States on this point based on the current CEP system in effect. A number of Member States supports each of these positions:

Support of the view of making the CEP mandatory for pharmacopoeial substances;

Opposition to the view of making the CEP mandatory for pharmacopoeial substances;

No need for making the CEP mandatory for pharmacopoeial substances.

## **Recommendations for change**

### **1. Single ASMF procedure including which competent authority to carry out the assessment, links with inspections**

#### **Drafting Group:**

Lead: Laura Galatti; Members: Teresa Dannert, Maryam Mehmandoust, Gernot Hirn, Susanne Keitel, Mathilde Geynet, Nino Mihokovic

General principle:

- ASMF – as a stand-alone dossier
- Mandatory centralised/centrally coordinated procedure for assessment and inspection

Relevant Committees, Working Parties (e.g. CHMP; CMDh, QWP, BWP, CVMP, CMDv, ASMF Worksharing Group) and stakeholders (EDQM) should be consulted on details of these procedures. The criteria to allocate/set the assessors/Rapporteurs/lead MS should be thoroughly set. Possibilities to contribute to assessment and comment should be clearly defined as well as an avenue to discuss divergent views on assessment.

#### **1.1. Background:**

Currently in EU a specific ASMF for chemical active substances may be submitted in relation to multiple applications for marketing authorisations for several medicinal products in one or more Member States. Once marketing authorisation is granted, ASMF revisions have to be submitted as variation procedures for each authorised medicinal product that uses the same ASMF separately. Accordingly, each ASMF version may need to be reviewed multiple times by one or more Competent Authorities. Consequently, the workload for all involved parties is increased, oversight of ASMFs is reduced and inconsistent decisions may be made by competent authorities. The latter actually may trigger the next revision of the ASMF resulting in frequent ASMF updates.

The ASMF worksharing (WS) procedure established about 10 years ago has reduced the above mentioned burden from ASMF procedures and has been a valuable learning exercise which was demonstrated to be very useful. However, the full extent of workload reduction could not be obtained as the current ASMF WS procedure is strongly recommended, but not mandatory (i.e. there is no legal basis for it). Another major problem identified in the ASMF WS procedure is the floating rapporteurship for assessment of the ASMF, as this is linked to the procedure/medicinal product in support of which the ASMF is referred to. Thus, having an ASMF separated from the Dossier is important to make a more efficient ASMF procedure. A Mandatory centralised/centrally coordinated procedure for single assessment of ASMF with the meaning that one Competent Authority would be in charge of coordination of assessment of the whole lifecycle of the active substance (AS) is highly recommended, even necessary.

Mandatory centralised/centrally coordinated stand-alone procedure for single assessment of ASMF (mandatory centralised ASMF assessment) is a necessity to build an efficient regulatory framework, since it would significantly reduce multiplication of work and contribute to the harmonisation of assessments as well. This proves also to be very efficient in case there are quality issues with an active substance, to identify quickly and address the issue in a centralised/coordinated way.

The MAH remains always the final responsible of its own medicinal product and Marketing Authorisation dossier. It is also responsible to update its own dossier in relation to the updates of ASMF submitting the related variations to the NCAs, regardless which Centralised/centrally coordinated stand-alone procedure will be adopted in the legislation.

## **1.2. Future:**

The assessment of an ASMF should be separated from that of the Marketing Authorisation Application or Variation Application. The ASMF would have to be a self-standing dossier, submission and assessment of the ASMF would become independent. **Change in legislation is necessary.**

- The requirements of an ASMF holder when applying for a mandatory centralised ASMF assessment should be thoroughly set in the future and verified e.g. based on inspection plan. It is recommended to have an active program of inspection and follow up as the QP declaration system, though necessary, however has showed some limitations. A formalised system at EU level would be necessary.
- Assessors/Rapporteurships have to be allocated. Criteria used to allocate them should be set. The NCAs should commit necessary resources to support the system.
- The structure and details of the future procedure have to be elaborated, e.g. assignment of a procedure number, timetables and assessment phases.
- The corresponding IT systems at EU level have to be available (for dossiers and assessment reports) whereby existing systems can be used.
- Access for all competent authorities to restricted/applicant's parts and assessment reports should be ensured. Thus, in case of any quality defects declared (e.g. such as detection of nitrosamines, azide impurity etc...) the NCAs could react promptly by having access to the whole and complete information.
- Fees, fee reductions and waivers would have to be established, so that the respective fee must cover all the costs.
- The restricted/applicant's part structure of the ASMF should be maintained however its scope might be revised in further discussions and in view of additional considerations (e.g. Lessons learnt from presence of N-nitrosamine impurities in sartan medicines).
- A procedure should be put into place to consider also veterinary products and the consequences taking veterinary legislation and guidelines into account. Whatever happens on the human side in this area, it can be expected that it will have significant implications also for veterinary medicines since most APIs are used in both human and veterinary medicines and many API suppliers supply both markets. Whatever direction is taken on human side (i.e. CEP-like procedure or Centralised rapporteur procedure), it should be considered with both human and veterinary products in mind. If a system is developed that is only applicable for human APIs, it is likely that some, perhaps significant numbers, of API suppliers will discontinue supply for veterinary medicines if the system for veterinary medicines is considered too complex/cumbersome in comparison with the new system for human medicines.
- Sufficient transparency of such procedures to both applicants / marketing authorisation holders and competent authorities is essential and has to be considered in the development phase of the procedure. Regarding CEP-like procedure, some Member States have identified issues on transparency regarding the current CEP procedure (ref. *Cons* section of CEP-like procedure as detailed further in this document). EDQM reported that it has identified ways to address this

specific aspect related to transparency of the current CEP procedure, in particular by changing details of information mentioned on the CEP document, and by implementing an open (applicant's) part for CEPs or an equivalent document that would be shared by the CEP holder with the MAHs. The EDQM is ready to adapt further the procedure if needs are identified.

The new procedure should be mandatory within the meaning that no other parallel submission would be possible to EMA/NCAs. Regarding the already assessed ASMF a way to add them in the project for future updates needs to be established.

### ***1.3. Potential alternatives for mandatory centralised ASMF assessment procedures:***

#### **CEP-like procedure: administration / coordination (of assessment and inspections) to be performed by a central entity (EDQM).**

General comment: This procedure would need to be established and designed. It doesn't mean that the current CEP procedure should be adopted as is. It should be amended based on Pros/Cons reported on the current CEP procedure (e.g. issues on transparency, involvement of MS in assessment, decision making).

#### Pros:

- EDQM already has years of experience in coordinating certification of chemically synthesised pharmacopoeial APIs and inspections of API manufacturers. Respective processes, including nomination of assessors, allocation of dossiers to assessors, assessment of CEP dossiers, certification, OMCL testing and inspection are established. If another entity than EDQM would be tasked with coordinating this future procedure, then some of the current practices could be adopted; thus, the CEP-like procedure would function similar to the current CEP system, but would need to be discussed between relevant stakeholders as recommendations for improvement of the current CEP system have been identified.
- EDQM databases could be used to report ASMF and assessment reports.
- Assessment of all chemically synthesised active substances would be coordinated by EDQM, i.e. one central authority. Compared to running parallel systems (i.e. mandatory centralised rapporteur procedure coordinated by EMA and current CEP procedure coordinated by EDQM in parallel) no inefficiencies or problems as identified in the 'cons section' of the mandatory centralised rapporteur procedure would occur.

#### Cons:

- A transparent system should be envisaged and guaranteed where the complete data will be available to all assessors in Europe and involvement of all assessors in the NCAs should be ensured. The current CEP system is not sufficiently transparent to NCAs or to the MAH/MAAs. So far, the NCAs do not have access to the dossiers submitted to EDQM. Not only CEP dossiers should become available to EMA/NCAs but also a system should be thought that an equivalent to the open (applicant's) part of the ASMF be available to the MAH.
- Regarding the lifecycle assessment of the ASMF, using different assessors for every update of the ASMF-as currently organised in the CEP system is considered more time consuming for assessors. In addition, as assessors change in different rounds of assessments, the global view on a given dossier remains only with EDQM and not with assessors and NCAs. Some Member States would like to have the possibility to comment and to be involved in decision making.

## **Centralised – rapporteur procedure: administration / coordination (of assessment and inspections) to be performed by the EMA**

General comment: A formalised procedure for communication of new information (e.g. impurities) relevant to Ph. Eur. monographs needs to be established from Rapporteur to EDQM.

### Pros:

- A system like the current Centralised procedure could be established for ASMFs. The centrally coordinated single assessment procedure can be handled by the EMA. However, the assessment of the whole lifecycle of the ASMF should be performed by one NCA acting as Rapporteur, a Co-Rapporteur can be also nominated in view of having a robust assessment by performing a critique of the AR provided by the Rapporteur. Alternatively, the assignment of Rapporteurs could follow a PSUSA-like approach.

EMA has a long standing experience of coordination of different procedures and topics within the EU: centralized procedure, plasma master file procedure, PSUSA procedures, even for non-centrally authorized products i.e MRP/DCP and purely nationally authorized products for PRAC signals, nitrosamines, organization of different working parties, etc.

- The rapporteurship on different APIs can be divided between Member States, therefore experience of assessment and overall view on different aspects of assessment will remain with EMA/ NCAs and their assessors. There will be no loss of knowledge and insight of NCAs about chemical APIs.
- The dossiers and ARs can be available to all Member States through available repositories such as the Common repository for dossiers or the CTS ASMF module that serves currently for uploading ARs. However, a new IT tool/repository specific to master file procedures could be also set up.

### Cons:

- Running parallel assessment systems (mandatory Centralised – Rapporteur and current CEP system) for chemically synthesised APIs would be inefficient and may cause problems, e.g.
  1. CEP procedures currently are the main source of information to ensure Ph. Eur. monographs are updated and state-of-the art. A decline in CEP applications following implementation of a mandatory Centralised – Rapporteur procedure for all chemically synthesised APIs would thus negatively impact the Ph. Eur. itself.
  2. if ASMF holders would be allowed to choose freely between EU certificate and CEP this would create an unfavourable competitive situation between EU authorities and EDQM.

## **1.4. Proposed solutions – in legislation**

The appropriate legal basis should be established, to allow for a mandatory centralised ASMF assessment, which should consider the following elements:

- The Authority responsible for the coordination of assessment of the whole lifecycle of the ASMF (depending on which of the options presented above is put in place).
- A link between assessment and inspections is needed. Emphasise that assessment should routinely include the evaluation of a potential need for an inspection from a dossier perspective.

- Separation of the ASMF/assessment of ASMFs from MAAs.
- Mandatory character of the new procedure.
- In case of suppression of the link with the Marketing Authorisation, it is important to clarify who is legally responsible for the quality of the active substance. The MAH will continue to be responsible for their product, including the active substance they use. It would be important to stress this in the legislation.

At this moment the only place in legislation, the current concept of the ASMF procedure is referred to is Directive 2003/63/CE annex I to 2001/83/CE, Part 3, 3.2. Content: basic principles and requirements, intend (8) that need to be amended.

Given the percentage of active substances coming from outside the EEA, it would be crucial for ASMF holders outside the EEA to be able to apply for a mandatory centralised ASMF assessment procedure.

### ***1.5. Proposed solutions – in guidance***

Substantial revision/change of the guideline on ASMF procedure CHMP/QWP/227/02 Rev 4/ Corr \* and respective QWP and CMDh Q&As in the 1<sup>st</sup> stage. Revision of guideline on Summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97 Rev 1 to include guidance on data to be provided to the MAA/MAH for sake of transparency. Revision of Chemistry of active substances (chemistry of new active substances) guideline EMA/454576/2016.



## 2. Extending scope and application of Master File concept to some raw and starting materials, some excipients, biologics, etc.

### Drafting Group:

Lead: Nino Mihokovic; Members: Mats Welin, Barbara Bonamassa, Maryam Mehmandoust, René Thuermer, Gernot Hirn

### General comment

The Master File approach should be optional in the meaning that an applicant could choose either the Master File approach, or to submit the full data in the dossier.

However, should an applicant choose the Master File approach, this should be under a mandatory centralised Master File assessment procedure in analogy to the respective procedure for active substances as described in section 1, considering the details discussed above.

### 2.1. Approach 1

#### Master file concept in legislation/guidance

To amend the legislation with the concept of master files in general consisting of closed and open parts and to emphasize the need for the MAH to take overall responsibility for the product and leave it to EMA / EC to manage the type of master file (listed below) + scope of open and closed parts via a guideline. This would future-proof the legislation and allow flexibility in expanding the concept when a business case arises.

### 2.2. Approach 2

To define extended master files in legislation as per below.

	Recommended inclusion	Not recommended inclusion	Further discussion could be needed
starting materials (viral vectors, cell lines and cell seeds, plasmids)			x
starting materials (chemicals)		x	
(critical) raw materials (media components, enzymes or growth factors)			x
raw materials (other than starting materials – for chemicals)		x	
API intermediates (when intermediate is chemical active substances by itself or used in conjugation of biologics)	x		

API intermediates of chemical active substances		x	
biologicals		x	
finished product intermediates		x	
excipients (or mixtures such as printing inks, co-processed excipients)		x	
flavouring			x
novel excipients	x		
adjuvants	x		
packaging		x	
analytical methods		x	
radiopharmaceutical precursors	x		

### **2.2.1. Extension of scope to include starting materials (viral vectors, cell lines and cell seeds, plasmids).**

Whereas certain starting materials e.g. production cell lines and cell seeds, which are well established and commercially available could potentially benefit from a Master File concept, the feasibility for other starting materials such as plasmids, viral vectors used in the manufacture of genetically modified cells could be more difficult. In most cases comprehensive knowledge of the development and controls of the starting material might be essential to the development and quality assurance of the active substance and therefore this information should be fully available or owned by the active substance manufacturer/MAH.

This point would need further technical discussions and considerations in order for it to be included in the extended Master File scope.

### **2.2.2. Extension of scope to include starting materials (chemicals).**

The starting materials for chemicals should not be included/considered in the extended scope of Master File concept. Comprehensive information should be available to the active substance manufacturer as a basis for control strategy and selection of starting material.

### **2.2.3. Extension of scope to include (critical) raw materials (media components, enzymes or growth factors).**

This point would need further technical discussions and considerations in order for it to be included in the extended Master File scope.

#### **2.2.4. Extension of scope to include raw materials (other than starting materials – for chemicals).**

The raw materials for chemicals should not be included/considered in the extended scope of Master File concept. The only information required for such materials is related to quality control at the site of the intermediate or active substance manufacturer and a master file approach is not seen as feasible.

#### **2.2.5. Extension of scope to include API intermediates (when chemical active substances in themselves and used in conjugation of biologicals).**

Today a chemical substance which is authorised on its own can use a ASMF while this is approach is not allowed if it forms part of an antibody-drug conjugate (ADC) as this resulting active substance is a biological substance which currently is not within the scope of ASMF. Allowing such a system would facilitate the use of drug components manufactured by other suppliers. The possibility to use the ASMF for the chemical part of a biological molecule would avoid unnecessary multiplication of work.

Therefore, it is recommended to extend the scope of the Master File concept to include active substance intermediates when the intermediate can be itself a chemical active substance or when the intermediate is used in conjugation of biologicals.

#### **2.2.6. Extension of scope to include API intermediates of chemical active substances.**

The intermediates of chemical active substances should not be included/considered in the extended scope of Master File concept. Comprehensive information should be available to the active substance manufacturer as a basis for control strategy. This is to allow assessment of the overall control strategy. If part(s) of this information would be provided in separate master files, the assessment becomes too fragmented.

#### **2.2.7. Extension of scope to include biologicals.**

The extension of the scope of the Master File approach to include biologicals is not recommended due to complexity and inherent variability of biological active substances.

#### **2.2.8. Extension of scope to include finished product intermediates.**

The finished product intermediates should not be included/considered in the extended scope of Master File concept. Appropriateness of intermediate quality depends on the quality of the used active substance sourced from (a) specific active substance manufacturer(s) and the quality target product profile of the finished product and thus cannot be assessed on its own.

#### **2.2.9. Extension of scope to include excipients (or mixtures such as OraSweet, printing inks, co-processed excipients).**

As most excipients are currently well covered by Ph.Eur. monographs or Regulation 231/2021 (for colourants), a question is raised on the added value of including these in the extended Master File concept, as there wouldn't be commercially confidential information that would need protecting.

There are ongoing discussions on the definition of co-processed excipients (which could be classified as finished product intermediates as well). While co-processed excipients are widely used by finished product manufacturers there is currently limited information about co-processed excipients provided by the manufactures. If the Master File procedure was also applicable to co-processed excipients more

information on quality and safety about co-processed excipients could be easier to obtain, as they are not properly regulated yet. However, as these discussions are ongoing, it could be premature to include them in the extended Master File concept at this point.

Currently there is a suggestion to review the definition of excipients as per the Concept Paper on Core definitions. In case a third category of functional excipient is introduced, depending on its scope, there could be value of expanding the Master File scope to it. However, as these discussions are ongoing, it could be premature to include them in the extended Master File concept at this point.

#### **2.2.10. Extension of scope to include flavouring.**

There has been and there is some need to submit few information from suppliers of flavours as it was/is considered commercial confidential information (CCI) but the extent of required information is very limited. Confidential information on the composition of flavours is indeed sometimes submitted separately by the manufacturer to the competent authority. A centralised way of administration of approved flavourings could be helpful but organising a full master file procedure is disproportional to the limited data concerned. This point would need further technical discussions and considerations in order for it to be included in the extended Master File scope.

#### **2.2.11. Extension of scope to include novel excipients.**

For novel excipients full details of manufacture, characterisation and controls with cross references to supporting safety data should be provided according to the active substance format. Therefore, a master file procedure would be reasonable and is already established in other regions (e.g. USA, Canada).

#### **2.2.12. Extension of scope to include adjuvants.**

Several newly developed adjuvants that can be used in a variety of vaccines, i.e. of interest to many different companies can be identified in the system. These are often developed by manufacturers specialized in adjuvants and who may not be willing to share full documentation with the vaccine manufacturer. Extending the master file concept to adjuvants could therefore facilitate the use of such adjuvants.

It is important to emphasize that the manufacturer who makes use of a Master File for an adjuvant from a competitor or commercial supplier becomes aware of changes in the manufacturing of the adjuvant in order to trigger a check if the modified adjuvant works with his product. The National Competent Authorities/EMA may not accept that particular information has not been disclosed to the Applicant/MA holder. In such cases, and In line with the current ASMF guideline, the National Competent Authorities/EMA may ask for an amendment to the open part.

#### **2.2.13. Extension of scope to include packaging.**

For packaging materials, the information regarding quality control at the site of the finished product manufacturer and confirmation of compliance with Ph.Eur. monographs, if applicable, is generally required to be included in the ASMF / dossier. With respect to that there is no problem regarding confidential information, which packaging material manufacturers would not be willing to share. For some packaging materials and dosage forms information regarding functionality and/or compatibility of packaging materials have to be addressed too. However, this needs to be done product specifically and thus cannot be covered by a Master File procedure. A Master File procedure for packaging materials is thus not needed.

#### **2.2.14. Extension of scope to include analytical methods.**

For analytical methods a sufficiently detailed description to allow OMCLs to perform the method and method validation data are required to be included in the ASMF / dossier. A Master File procedure for analytical methods is thus not needed.

#### **2.2.15. Extension of the scope to include radiopharmaceutical precursors**

Regarding radiopharmaceuticals, some active substances cannot be isolated and control tested because they are generated *in situ* during the manufacturing process of the finished product. In such cases, the closest precursor(s) that can be isolated and control tested is(are) usually called precursor(s) and can be the subject of an ASMF, as it is the only substance where the quality of the active ingredient present in the finished product can be controlled. They cannot be considered starting materials or intermediates. This should be recognised in any future regulatory framework.

#### **2.3. Removal of VAMF from legislation**

Removing the VAMF concept from legislation is proposed as it has in practice not been used. Additionally, the 2nd step, to formally submit a product specific variation following the approval of a change to a VAMF was found too cumbersome.

#### **2.4. Proposed solutions – in legislation**

The newly proposed extension of the scope of the master file / mandatory centralised Master File assessment (as proposed in Section 1 of this Concept Paper) and the interplay with a marketing authorisation- or variation procedure would need legal basis.

Manufacturers of these materials (inside and outside the EEA) would need to be able to apply for a master file / mandatory centralised ASMF assessment.

Amendment of 2003/63/CE annex I to 2001/83/CE would be needed.

#### **2.5. Proposed solutions – in guidance**

Details of substances covered by the proposed extended scope of the master file- / mandatory centralised ASMF assessment and how the outcome of these procedures will be included in the course of a marketing authorisation- or variation procedure to be further addressed in guidance and Q&A document(s).

Revision of current respective guidelines and different Q&As would also be needed (e.g. Guideline on Active Substance Master File Procedure, Variation Guideline).

### **3. Interplay with CEP: Explore making CEP mandatory for chemical pharmacopoeia substances**

#### **Drafting Group:**

Lead: Susanne Keitel; Members: Maryam Mehmandoust, Nino Mihokovic, Susanne Stotter, Teresa Dannert

#### **3.1. Background**

The CEP procedure provides for a centralised assessment of pharmacopoeial substances and is well established since the beginning of the 90's; it combines the two important aspects of dossier assessment and risk-based GMP inspections, both of which are anchored in the current pharmaceutical legislation. CEP dossier assessment provides important information to the European Pharmacopoeia Commission on the potential need to revise a monograph and contributes to keeping the Ph. Eur. updated.

Three different viewpoints have been communicated from different Member States on this point based on the current CEP system in effect. A number of Member States supports each of these positions and their arguments are presented below. Furthermore, it is to be noted that the EDQM has already initiated a revision of the procedure and has conducted a broad stakeholder survey in 2020 for this purpose.

#### **3.2. Support of the view of making the CEP mandatory for pharmacopoeial substances.**

Taking into account the current workload of NCAs and stakeholders, it is an absolute need to use all available resources and current knowledge we have, as well as elaborate future possibilities, while avoiding limitation of well-established systems like the CEP procedure in the European regulatory network. The CEP procedure has demonstrated substantial benefits and is already in place since 1994. It saves time and costs for Industry and NCAs, avoids unnecessary multiplication of work and reduces resources and regulatory burden; it avoids increase in workload for all involved parties, reduced oversight of master files, inconsistent decisions and frequent master file updates. It provides for a harmonised assessment and routinely includes the question on the need for an inspection. Aspects that need to be assessed in relation to the specific medicinal product the CEP is used for, like elemental- or nitrosamine impurities risk assessment, can be addressed sufficiently in the active substance and finished product section of the dossier, as would be the case in a mandatory centralised ASMF assessment proposed in section 1.

Making CEPs mandatory for pharmacopoeial substances would solve current disadvantages of its optional use: a manufacturer of a given pharmacopoeial active substance can currently submit an ASMF to EU NCAs and at the same time apply to obtain a CEP from EDQM, with the risk of parallel dossiers for the manufacture of a given active substance at a given manufacturing site, potentially not identical from the beginning or deviating throughout their life-cycle, not to mention duplication of work.

It should also be mentioned that the CEP procedure is in place to provide the Ph. Eur. Commission with valuable information on the potential need to revise monographs. Even though according to Directive 2001/83, as amended, NCAs are obliged to inform the pharmacopoeia authority of impurities that are not controlled by a monograph they come across in MAAs, this is in fact very rarely done, while reporting any issues identified with methods described in Ph. Eur. or additional impurities identified is an integral part of CEP assessment. Hence a mandatory CEP procedure for pharmacopoeial substances

also endorses the development of Ph. Eur. and with that, improves quality control of medicines not only in Europe but worldwide. It is crucial to keep the Ph. Eur. up to date and competitive worldwide (e.g. United States Pharmacopoeia). Making the CEPs mandatory would have a positive effect on workload of the NCAs. Claims by some Member States that if CEP procedure is made mandatory for the pharmacopoeial substances, the NCA's are not able to assess API documentation are not appropriate as the quality assessors of all Member States are invited to become the external experts and TAB members of the CEP who actually make the decisions of procedures co-ordinated by EDQM.

An additional point that should be solved in the current legislation is the acceptability of ASMF and CEP in parallel for the same API produced using the same route of synthesis. The waste of resources can easily be solved by implementation of mandatory CEP procedure. Hence the revision of principles is absolutely needed and the current practice has to be changed taking into account the future targets and goals (single assessment, facilitation of authorisation etc.).

Some Member States claim that a mandatory CEP procedure for pharmacopoeial API would lead to a depletion of competences to assess active substance documentation at the NCA, since the majority of ASMF would move to EDQM for CEP procedure. To address this concern one proposal was to introduce a process similar to the current process for CP assessment by the EMA, where the EDQM would appoint two MS that would perform the assessment as Rapp and Co-Rapp instead of the current CEP assessment process. Additionally, the EDQM should establish a comprehensive system of inspections related to the CEP and increase transparency towards NCA by enabling us to see the submitted documentation (similar to Central Repository for CP procedures).

### ***3.3. Opposition to the view of making the CEP mandatory for pharmacopoeial substances.***

The option of making CEP mandatory for pharmacopoeial substances is not supported. The quality assessment of pharmacopoeial and non-pharmacopoeial substances is based on the same technical guidances, which in fact are all developed and adopted by the EMA and ICH. Therefore, there are no technical reasons for blocking access of pharmacopoeial substances to the ASMF centralised procedure. A mandatory CEP procedure does not facilitate flexibility for companies and will potentially limit access to medicines and cause shortages.

In addition, it should be taken into account that there are substances that do not have a Ph. Eur. monograph currently, but they can have it in the future. This can have further consequences that would need to be considered, e.g. whether the ASMF holders will be obliged to apply for a CEP since the moment that the API monograph is in force; which would be the technical grounds for such a change; whether this change is considered beneficial for the European regulatory framework.

On the other hand, if the CEP procedure is made mandatory it will imply that the NCAs, which are responsible for the authorisation of medicinal products, will not be allowed to assess the quality of the API of the majority of the medicinal products in the European market. The management by the NCAs of any quality defects linked to the API could be compromised.

Some Member states claim that the CEP system, as currently built cannot respond to the challenges of a globalised and at the same time fragmented supply chain of medicinal products. The ultimate responsibility for the medicinal product and the API used remains in EU legislation with the MAH. Where the format/model of the system does not allow sufficient transparency to the MAH then it can be considered contradictory to the needs and not well adapted to the new challenges.

The issue raised under 3.2. on disadvantages of having parallel ASMFs and CEPs can be addressed without making the CEP mandatory, by revising the ASMF Guideline to exclude the possibility of

maintenance of both ASMF and CEP for the same active substance/same manufacturer/same route of synthesis.

### **3.4. No need for making the CEP mandatory for pharmacopoeial substances.**

It was noted that if the new ASMF assessment system would work well, making CEPs mandatory for substances covered by the Ph. Eur. should not be necessary.

### **3.5. Proposed solutions – in legislation**

Making the CEP mandatory for pharmacopoeial substances would need a legal basis and would trigger a change in the variations regulation. In addition, it would be beneficial to highlight the responsibility of the finished product manufacturer, not only for their medicinal product, but also for the active substance they use, in the legislation again.

### **3.6. Proposed solutions – in guidance**

- While there is no full agreement whether sufficient guidance is already available, there is a clear agreement that there will be a need to update a number of texts to address the mandatory character of the CEP procedure, e.g. the guideline Summary of the requirements for active substances CHMP/QWP/297/97 Rev 1, the ASMF guideline and relevant Q&As to translate the above considerations and to revise the Chemistry of active substances (chemistry of new active substances) guideline EMA/454576/2016. It should also be clear in the variations guideline that a new CEP version should be applied for immediately and product specific issues should be applied for in addition.
- Alignment of different EU texts between a future Master file procedure for the active substance (under section 1 of this paper, master file assessed before the MAA) and CEPs.

### **3.7. Other necessary actions**

As outlined before, the content of the CEP needs to be revised and provide more information to users – an activity underway and triggered by a broad stakeholder survey conducted by the EDQM in 2020 to design the “CEP of the future”. This should include increasing the transparency of the CEP procedure by routinely making CEP dossiers themselves available to competent authorities, e.g. via the EDQM CEP database, and by providing an open part, similar to the ASMF, to users.

Ideally, all MS would contribute by nominating assessors and inspectors, where applicable. In addition, potential benefits of including all MS as CMS should be looked into in detail.

Aspects related to the timelines for changing from an ASMF-procedure to a CEP-application, once a CEP procedure becomes mandatory, would also need to be resolved. It would be impossible for an active substance manufacturer to immediately change procedure from an ongoing ASMF-procedure to CEP-application for active substances that have their first version of the monograph published. A reasonable implementation time has to be defined.

Costs for national competent authorities for involved assessors (and inspectors) have to be fully covered by specific procedure fees. However, in this context it may be necessary to look also into the fee structure of marketing authorisation applications referring to a CEP to avoid double payment of the cost for active substance assessment by the applicant.



## 4. EDQM's perspective

EDQM has not been included in the drafting of this Concept Paper. EDQM provided comments on the early draft, which were considered for the creation of the Mature draft interim paper that was sent to the EC.

Following this stage, it was decided to include EDQM's representative in the Drafting Group and their views are provided in this section.

Based on EDQM experience with the CEP procedure, the EDQM is of the opinion that centralisation of ASMF assessment is key to build an efficient regulatory framework, since it would significantly reduce duplication of work and contribute to harmonising assessments related to API quality. A CEP-like procedure has proven to be a successful, collaborative model, and this kind of process is well-known by API manufacturers via the current CEP procedure.

With regards to section "3. Interplay with CEP", the split positions are noted, however the EDQM supports the concept of using the CEP procedure as single ("mandatory") tool for the assessment of pharmacopoeial (Ph. Eur.) substances, in a framework where there would be a single, centralised system for ASMF assessment. This would make best use of the CEP procedure, provide clear scopes and responsibilities for both the ASMF and the CEP procedures and would further avoid any potential for duplication of work. In addition, the close relationships between the CEP and the Ph. Eur. contribute significantly to maintaining the Ph. Eur. monographs up-to-date, thus ensuring that they reflect the quality of products on the market, therefore using the CEP procedure for pharmacopoeial substances would contribute to maintaining a strong European Pharmacopoeia at international level.

Since the CEP procedure is well-known and widely used, some gaps have been identified (cf Sartans Lessons Learnt and cons expressed in this Concept Paper). These gaps are currently being addressed through the EDQM project "CEP of the future" which should be implemented in 2023. The EDQM can further adapt its processes to fit and contribute to building a future efficient regulatory system, for the benefit of industry, regulators and public health.

The chair of the CEP Steering Committee and the Director of the EDQM have written to the European Commission to express these views.

## 5. European Commission Questions and Responses by the EMA/EDQM

We have had an internal discussion in the team on the draft concept paper on ASMF which gave rise to some questions and ideas:

- **To what extent are the assessments of ASMF and CEP the same? How much are the ASMF and a dossier for a CEP alike?**

The same CTD content of 3.2.S. applies to ASMFs and CEP dossiers. The ASMF format is divided between open and closed part (open part to be available to the MA holder) but the CEP dossier submitted to EDQM is generally a single dossier containing all the information and is not divided in two parts. Nevertheless, EDQM Certification accepts that an ASMF format be submitted by CEP applicants if they are willing to do so.

Content of the dossiers and assessment of ASMFs and CEP are fundamentally the same, however there can be some differences, for example ASMF will generally include stability data for the active substance whereas this is not always included in the CEP dossier.

The provisions of the guideline 'Chemistry of active substances' apply, in principle, to assessment of all APIs in EU regardless of the way of submission of data. In addition, the ICH and other EU guidelines along with relevant Ph. Eur. texts are applicable to ASMFs and CEPs.

For a pharmacopoeial substance vast majority of data are identical (CEP dossier and ASMF) and are assessed in an identical way. CEP dossier is assessed in the course of CEP procedure at EDQM while the ASMF is assessed in the course of the specific MA procedure. Certain data additionally need to be assessed in relation to the finished product, and in case a CEP is used these remaining data have to be submitted in the marketing authorisation application because the CEP dossier is submitted independently from the finished product dossier.

However, the main difference in assessment has to be seen between pharmacopoeial and non-pharmacopoeial substances instead of between CEP/ASMF assessment.

For non-pharmacopoeial substances or new active substances larger amount of information is required and to be assessed to justify specifications for impurities or physico-chemical attributes. Non-pharmacopoeial substances are outside of the scope of the CEP procedure.

- **What would be a reasonable timeframe for single assessment of ASMF? How long does it take under current framework to assess an ASMF?**

If an ASMF assessment is taken alone and out of any procedural timeline, according to the experience of assessors the following can be expressed:

the assessment of an ASMF depends on one hand whether the active substance and its manufacturing are simple or complex and on the other hand on completeness of data presented by the ASMF holder. However, from a general point of view the assessment of an ASMF until final acceptance can be performed in 2 or 3 rounds of assessment.

For the first round of assessment and to give an idea, it goes from 3-4 working days (a simple AS) to up to 8-10 working days (for a complex AS or new AS) and for new technologies with regulatory flexibility (Design Space), continuous manufacturing, etc. it can go up to nearly 15 working days.

In response to the second part of the question i.e. under the current framework, an ASMF is still part of Marketing Authorisation in EU. Thus, it is assessed during the assessment of the DC/MR/CP

procedures with the related timeframe which is 210 days for DC and 60-90 days for MR (in case of MR procedures the ASMF had already been authorised by the RMS during the related national procedure). Please consider also that 210 days take into account the timeline procedure including initial assessment from RMS/rapporteur (70/80 days), comments from CMSs and further assessment of the Applicant responses during the single steps of the procedure.

Therefore, no specific timeframe for assessment of an ASMF is foreseen currently as this is considered as part of the DC/MR/CP procedures aimed to authorise the medicinal product. However, the variation regulation provides a good reference regarding time for assessment of an ASMF. Introduction of a new ASMF is considered a Type II variation with a 60 day (40 days for the RMS) initial assessment timetable, +30 days for the assessment of the MAH responses, which could be applicable to the single assessment of the ASMF too.

- **To what extent does an ASMF already assessed or a CEP reduce (quality) assessment time for the competent authorities?**

An ASMF already assessed within the ASMF Worksharing procedure or a CEP significantly reduces the assessment time and resources of assessors assessing the API part of dossier module 3 (part S of the MAA).

The reduced time for assessment in a MAA or MAV is equivalent to the time spent and described under Q2 for assessment of a new ASMF in different situations.

It should be taken into account that even if there is a CEP or an already assessed ASMF, the impurity profile, physico-chemical characteristics and microbiological aspect of the API should be considered and assessed in relation to a specific medicinal product and its intended use within the applied MAA or MAV. This part will always remain to be assessed.

- **Instead of making the CEP mandatory if there is Ph.Eur. monograph, perhaps a cascade could be envisaged:**

1. **CEP, if the product has a Ph.Eur. monograph**
2. **ASMF, if justified or if the product has no monograph**
3. **Full Module 3 with MAA, if justified**

**Such a cascade would maintain some flexibility for companies.**

Introducing a cascade instead of making the CEP mandatory could possibly be an alternative to formally making the CEP mandatory.

However, use of full information in Module 3 is discouraged as it would be difficult to avoid potential duplication of work in case the same data is submitted in the context of another MAA.

In case of establishing a cascade, it needs to be clearly defined and unambiguous rules need to be determined in which cases the CEP has to be chosen and in which cases ASMF or full Module 3 are a possible option. Consequences and measures to be taken in case of neglecting these rules need to be specified.

Finally, we would also need to make it unquestionably clear that duplication of submission (ASMF and CEP in parallel) is not accepted.

In case of absence of clear and specific rules for the cascade competition between CEP and ASMF and duplication of submission (ASMF and CEP) seems to be unavoidable.

- **What does a CEP cost? And how are the NCA assessors remunerated for their assessment for CEP?**

Currently the fee paid by API manufacturers to get a new CEP are 5000 Eur for most of the cases (e.g. they are different for TSE assessment). There are also fees to be paid for revisions of CEPs.

Currently contracts of collaboration between the EDQM and national agencies are in place or may be put in place and assessors are remunerated (in addition to the reimbursement of travel expenses/per diems when they come to the EDQM), however the current remuneration still may not cover all agencies costs. In the future, the fee structure can be changed and the EDQM is ready to increase the remuneration of assessors in order to cover the agencies costs.

- **How to avoid competition between ASMF single assessment and CEP based on price of procedure?**

In case a cascade, as discussed in question 4, is introduced, this would avoid the competition between CEP and ASMF single assessment.

- **For expansion of the master file concept to other areas, is the assessment of those master files coordinated by EMA?**

This point would need to be agreed by relevant stakeholders. Further information on the scope and number of affected substances would need to be gathered which would provide insight into which institution would be best placed to coordinate the assessment.

- **How should already assessed ASMF be added to the single assessment procedure?**

Due to workload involved a staggered or a risk-based approach on whether there is a need to include an ASMF into single assessment should be agreed.

Inclusion could be done immediately or at the time of next review/assessment.

A transition period might be needed and should be carefully considered involving relevant stakeholders.

- **Are you aware of any restrictions in the new Veterinary Regulation that would hinder a new system on the human side?**

The drafting group is not aware of any restrictions in the new Veterinary Regulation that would hinder a new system on the human side.

With respect to the ASMF procedure, there is no change in the new Veterinary Regulation 2019/6, i.e. the ASMF procedure remains unchanged for veterinary products as it was under previous Directive 2001/82 and respective Annex I. In principle, the ASMF procedure is now identical to that applied on

human side (see Commission delegated regulation (EU) 2021/805, i.e. Annex II to Regulation 2019/6, section 2.IIC1 (3)).

Regulation (EU) 2019/6 (Article 125) and Regulation (EU) 2021/805 also make reference to the EDQM certificate of suitability procedure, which is currently identical for human and veterinary medicines. These references are quite general and should not impact on any future system for human medicines but if there were significant changes to the EDQM CEP procedures they would need to remain compatible with the provisions of those regulations.

So the veterinary side will not hinder the revision of the legislation on human side but there will be consequences if the new system is developed considering only the human products as we already indicated in the CP on ASMFs under point 1.2.

Perhaps some of these questions/ideas can be considered in the final version of the concept paper.

## 04. Concept paper for EC on **New manufacturing methods**

**Main theme:** Adaptation of basic legislation to new manufacturing methods to avoid regulatory gaps and ensure appropriate oversight of a future-proof legislation – outline of technical aspects that would need to be covered.

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic leads	Experts from EMA/HMA
Drafting Group	Experts from QWP, BWP, GMDP IWG, CAT, CMDh, EDQM and EMA

This concept paper addresses the following topic in the field of new manufacturing technologies:

- Decentralised manufacturing
- Manufacture of personalised medicines
- Continuous manufacturing/innovative manufacturing methods
- Impact of Pharma 4.0 on manufacturing

Implications on manufacturing authorisation and the impact on batch testing and release have been considered when addressing the above topics.

In all topics the need for revising the current GMP batch definition has been raised

A definition of ‘batch’ can be currently found in several documents. In Directive 2001/83, the batch definition is given in the frame of the control of the finished medicinal product. GMP Annex 16 mentions in addition "the term in particular denotes the batch of product in its final pack for release to the market". Consideration should be given to harmonise them and have a single overarching definition in relevant guidance that could embrace future necessities. This could be then further elaborated in other specific guidance documents (e.g. personalised medicines) as required.

As an example, in the case of personalised medicine with finalisation of manufacturing close to the patient, the control of the finished product could be managed differently than traditionally done, and the fraction of the production expected to be homogeneous would not comprise the last manufacturing steps. A batch, within current understanding, could possibly only be defined for the constant part or even only for inputs/starting materials. Therefore, in order to leave room for flexibility in cases where the product composition needs to be variable, the drafting group believes that the overarching definition should avoid linking batch definition with the finished product in its final packaging

# Recommendations for change

## 1. Decentralised manufacturing

### Problem statement

Currently, manufacture of authorised or investigational medicinal products must take place in a facility holding a manufacturing and import authorisation (MIA<sup>1</sup>), and every batch must be certified by a Qualified Person for release. Certain activities related to medicinal products (e.g., extemporaneous preparation, reconstitution) can take place in hospitals or other healthcare settings without the need for a MIA as long as they are not considered as manufacturing steps. This approach is modelled on a "centralised" manufacturing paradigm that has been the dominant model in the last decades especially for large scale production. The current system is that all the manufacturing sites are inspected and authorised and all are registered in the marketing authorisation

The advent of new therapeutic approaches that have features such as very short shelf-lives and which may be highly personalised (e.g., advanced therapy medicinal products, ATMPs; blood derivative products;), and new manufacturing modes (e.g., continuous manufacturing, CM) and technologies (e.g., additive manufacturing, 3D print of chemical compound) enables "decentralised" (local to the patient) manufacture and use of patient specific medicines. Further product types will be probably expected in the future as technology continues to advance in medicines manufacture and supply.

These paradigms of decentralised and/or personalised manufacturing presents new challenges since they require a shift away from existing regulatory frameworks that are designed to meet the regulatory expectations for large-scale centralised manufacture. For example, in decentralised manufacturing (DCM), some or even all manufacturing steps may occur at different locations, such as hospitals, pharmacies or even mobile units. Under the current EU legislation, all of these locations should hold manufacturing authorisations, a qualified person (QP), and GMP certification, with mandatory approval and follow-up authority inspections as prerequisite, and be registered in the marketing authorisation dossier. Changes to the dossier are subject to regulatory oversight. Increase of sites in DCM will result in higher or even an unsustainable regulatory burden for all stakeholders (applicant, marketing authorisation holder and regulators).

Currently, only the EU GMP guideline for Advanced Therapy Medicinal Products (ATMPs) includes reference to decentralised manufacturing; this envisages a "central site", which should be established in the EU. The central site is responsible for the oversight of the remote sites. To this end, the central site assumes, as a minimum, the following tasks: *"(i) ensuring that those involved in the batch certification and release process are adequately qualified and trained for their tasks, and (ii) performing audits to confirm that the batch certification and release process described in a Standard Operating Procedure (SOP) is complied with"; (iii) a written contract/technical agreement between the central site and the decentralised sites establishing the responsibilities of each party*<sup>2</sup>.

However, the current legislation or the existing ATMP guidance does not address the details associated with the decentralised paradigm, e.g., how decentralised (remote) sites should be registered in the Marketing Authorisation (MA) or clinical trial authorisation (CTA), whether a MIA is required for each remote site, whether a QP is required for each remote site, lifecycle management, etc.

### Proposed solutions

The legislation should incorporate a risk-based and flexible approach that will allow the manufacture of a wide range of medicinal products (e.g., ATMPs, blood derivative products, 3D printed chemical products etc.) in close proximity to the patient. The approach should recognise the need for manufacturing steps to be performed in decentralised locations as close to the patient as appropriate for the quality of the product as well as for the safety of the patients.

The regulatory system is proposed to be based on a **central site** that will be registered in the clinical trial or marketing authorisation application as holder of the MIA and **remote sites** which will be overseen by the Qualified Person of the central site. The central site will be responsible for overseeing all aspects of the remote sites manufacturing system including the addition of new remote sites and control of each manufacturing location and activities. The remote sites will be a wide range of primarily

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<sup>1</sup> [Directive 2001/83](#) <sup>2</sup> [2017\\_11\\_22\\_guidelines\\_gmp\\_for\\_atmps.pdf \(europa.eu\)](#)

<sup>2</sup> [2017\\_11\\_22\\_guidelines\\_gmp\\_for\\_atmps.pdf \(europa.eu\)](#)

healthcare facilities such as pharmacies, operating theatres, ambulances, and military field hospitals or other mobile units.

The central site will be subject to regular GMP inspections conducted by the relevant Competent Authority and remote sites will be inspected using a risk-based approach that will select a sufficient exemplar of remote sites in order to provide assurance that a satisfactory level of control is exercised by the central site over the remote manufacturing sites. It is proposed that the central site will be required to register the activities of each remote site with the Supervisory Authority. The Supervisory Authority may, based on a risk assessment, decide to carry out an inspection. If the need of inspection is identified, manufacturing/testing activity shall not begin until completion of the inspection. The central site shall communicate at least annually to the competent authority an inventory of the changes which have taken place as regards the information provided in the registration form. All the remote sites notified by the central site should be registered by the Supervisory Authority into a dedicated database.

It is important that there will be clarity around the criteria when a product will be eligible for DCM and the different modes to decentralised manufacture (e.g., personalised medicines, point of care (POC) medicines and mobile manufacturing modes). Only medicinal products with short shelf life or where there is a clear clinical advantage to administrate the product to patients at point of care should be eligible for DCM. The eligibility for DCM will be granted within the MAA/CTA review process.

A set of criteria need to be developed in Guidance to define the circumstances under which a product can be eligible for DCM (e.g. short shelf-life, etc.).

These considerations should be given in the legislation and in GMP/quality guidance to ensure that consistent regulatory interpretation is achieved across all member states.

## **1.1. Proposed solutions – in legislation**

### **I. The proposed change to the Directive 2001/83/EC should include:**

1. Change to title IV of Directive 2001/83/EC the required system for MIAs/QPs etc.

Specific provisions for DCM should be introduced in the current legislation so that MIA are not required for remote sites undertaking specific and described manufacturing/testing steps under the responsibility of the QP of the central site (adapt art 40 directive 2001/83).

The current legal framework should also be adapted with regards to the responsibilities of the manufacturing authorization holder to include confirmation that remote sites are operating in compliance with Good Manufacturing Practices and manufacturing/testing in accordance with the MA/CTA. (change of art. 46).

The duties of the Qualified Person responsible for oversight of the remote site(s) will need to be adapted so that manufacture/testing performed at the remote manufacturing site(s) is monitored and controlled in compliance with Good Manufacturing Practice and the requirements of the MA/CTA. (change of art. 51).

2. Supervisory System of DCM:

Currently, each manufacturing site requires a MIA issued by the Competent Authority after a GMP inspection. Applying the existing legislation requirements without adaptation of the current legal framework will result in excessive burden for National Authorities and regulatory barriers for manufacturers.

For this reason, a risk-based approach should be implemented for the supervisory system of DCM. In particular, there should be a system that allows Member States to adopt a risk-based approach for the inspection of remote sites. This system should take also into consideration the cooperation among Member States in the coordination of inspections of remote sites within the EU (revision of art 111 directive 2001/83).

A registration process similar to the one implemented for APIs should be in place for the notification of remote sites. Addition of specific provisions for the registration of remote sites should be added in the Directive in order to describe the following process:

The central site must submit the registration form to the competent authority. The competent authority may, based on a risk assessment, decide to carry out an inspection. If the competent authority notifies the applicant that an inspection will be carried out, the activity shall not begin before the competent authority has notified the applicant that they may commence the activity. If the



competent authority has not notified the applicant that an inspection will be carried out, the applicant may commence the activity. The central site shall communicate at least annually to the competent authority an inventory of the changes which have taken place as regards the information provided in the registration form

In the context of the registration process of the remote sites, in order to increase the collaboration among NCAs, the implementation of an EU repository of remote sites providing an oversight of the involved sites to Supervisory Authorities, is also suggested. The registration form will be also linked to the MIA of the central site.

The concept of “**control measures**” could be also introduced in the legislation (art. 111 see concept paper for inspection subtopic reliance). Instead of having on-site inspections the Competent Authorities might decide to use distant assessments or rely on inspections performed by other Member State Competent Authorities.

The proposed supervisory system as part of the legal framework is intended to give a feedback mechanism from inspection to marketing dossier in order to ensure that there is no loss of regulatory oversight regarding post-approval changes.

3. CTD: Module 3 will describe the manufacturing/testing activities performed at the remote sites and where the certification and batch release process is performed at the central site

Revision of 2001/83/EC to allow variable product compositions (personalised) and wide batch size ranges (orders of magnitude) and to allow that remote sites will not have to be registered in the dossier. However, a declaration by the Qualified Person (QP) responsible for certification and batch release that states that all the remote sites operate in compliance with GMPs is required. The QP declaration might be submitted with the initial application and on regular basis (annual update) in order to update the list of remote sites involved in manufacturing/testing activities. The dossier will contain the MIA and GMP certificate for the central site. Guidance regarding module 3 expectations will need to be adapted, e.g., process consistency/validation, comparability, method qualification/validation. Of note, the manufacturing process steps/testing activities and the certification and batch release conducted remotely, will still have to be described in the dossier.

EC/1234/2008 (and associated guideline) need to also be revised to facilitate the above changes in 2001/83/EC.

4. The introduction of the decentralised manufacturing foresees no change at the existing legal framework for market surveillance, batch recall, sample and testing plan, pharmacovigilance.

## **II The proposed change to the Regulation (EU) No 536/2014 should include:**

Change of chapter IX (Manufacturing and import of investigational medicinal products and auxiliary medicinal products): Similar provisions for DCM as mentioned above should be introduced in this chapter.

### **1.2. Proposed solutions – in guidance**

It will be necessary to introduce a specific GMP annex for decentralised manufacturing and a new procedure in the Compilation of Community Procedures (CoCP).

Existing quality guidance will need to be reviewed to confirm applicability to DCM, its different modes and the impact on module 3 content.

#### **1. New GMP/GDP Guidance for DCM**

A new GMP/GDP guidance should be developed in order to introduce the DCM, criteria under which medicinal products will be qualified for the DCM (e.g., with short shelf-life, clinical advantage, batch size, etc.) and to establish the GMP/GDP requirements for the central site and remote sites. The batch release/certification process might also need to be redefined.

#### **2. New risk-based approach procedure for planning inspections and supervision of sites**

A new procedure in the CoCP should be developed in order to introduce different modes of DCM, definition of different type of remote sites and the risk-based approach for the selection of the site(s) to be inspected.

#### **3. Update of the existing guidance**

To update the existing procedure in the CoCP in order to clarify that the list of remote sites will be registered and regularly updated. In case of non-conformities identified during inspections, regulatory actions should be taken by the NCA against the central and the non-compliant remote site.

In case of remote sites located in different Member States, cooperation among the Supervisory Authority (SA) and the NCA of the Member States will be necessary. In case of multiple SAs, cooperation among SAs should be also considered. Guidance will define how this cooperation should be conducted.

#### **4. Quality Guidance and CTD Module 3 content**

Comparability assessment may be challenging for medicinal product manufactured via DCM especially for biological products and ATMPs. It will be necessary to update the Quality guidance in relation to how the comparability assessment is performed taking into consideration the different degrees of scale and complexity of the manufacturing process (different types of comparability exercises should be defined in the context of DCM).

GMP data from platform technologies and full-time digital connectivity will be presented in the dossier (e.g., aspect of GAMP could now form part of dossier). Other standards regarding digital communication/controls may also be important to be incorporated as well. Regardless this, GMP-based aspects of the manufacture will become part of the registered control strategy.

Expectations around process validation needed for a new MAA and when new remote sites are added (traditional process validation vs continuous process verification) should be defined. After the approval of the MA, the quality of the product must be monitored by the central site and verified by competent authority to ensure the state of control is maintained throughout the product life cycle.

Notice to applicant should be updated to ensure that manufacturing process steps conducted remotely will be flagged and described in the dossier.

## **2. Manufacture of personalised<sup>3</sup> medicines**

### **Problem statement**

According to current legislation, the finished product may only be as variable as the discrete presentations included in the marketing authorisation in terms of qualitative and quantitative composition of active substance(s) and excipients, size, shape, colour, etc. For example, if a medicinal product is authorised in the strengths 10 mg and 20 mg, the marketing authorisation holder may not market any strength in between 10 mg and 20 mg. The same applies for all remaining parameters that currently define the authorised discrete presentations of the finished product. In view of the current architecture, the information in the dossier on the manufacturing process of the active substance and finished product also obey the same strict margins of variability. Information on safety and efficacy follow accordingly.

Personalised medicines in this context are considered medicinal products that are adapted to specific and defined criteria of the patients.

Their manufacturing process can greatly differ. For example, they can be manufactured by means of an industrial process or in a bespoke setting (i.e. in a hospital laboratory/ at point of care). The manufacturing can either follow a traditional centralised model or a decentralised model.

Personalised medicines can contain chemicals, biologicals as active substances. Examples of personalised medicines include gene therapy including a vector targeting different single-patient specific tumour antigens, gene-editing technology adapted to target different patient-specific mutations, patient specific modification of monoclonal antibodies and other recombinant proteins and antisense oligonucleotides customised in a sequence-specific fashion to treat rare genetic diseases.

Personalised medicines have in common an adaptation of the medicinal product to the patient, in accordance with pre-defined and approved ranges and criteria. Such adaptations can be, but are not limited to, adaptations at the level of the starting material, raw materials, manufacturing process, excipient(s), formulation, dose and strength and/or administration procedure.

The current legislation does not cater for the variability associated with a personalised medicinal product regarding the starting materials, excipients, manufacturing process steps as outlined. In our

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<sup>3</sup> The term personalised medicines is used here to describe the customised product to the patient/patient cohort. Kindly note that in concept paper 5 additional considerations are provided.

view the new legislative proposal should provide for such variability, with associated data requirements (i.e. Annex I of Dir 2001/83) in support of the need for claimed variabilities with reference to the adaptations necessary at the patient level.

In order to allow for the variability within the same marketing authorisation of a personalised medicine and to define a threshold versus a new marketing authorisation, the concept of personalised medicines should retain a well-defined common element within the active substance and finished product which is linked to the commonalities resulting from the indication applied for. In the view of the drafting group the core concept and data requirements of the personalised medicine (i.e. the constant part + adapted part) can be accommodated in the "platform MA" approach (Reference is made to the platform proposal under the Concept paper 'core definitions').

The eligibility to operate under the personalised medicines concept should be defined and boundaries for personalised medicines should be set (criteria to consider in this context: size of patient group (max. number of patients per cohort), same/related indication). Specific criteria and the extent of manufacturing changes underpinning these principles are proposed to be further elaborated in guidance (see below). Products which are adapted by reconstitution, dilution based on body weight, or stratification are not considered to be part of personalised medicines if these products are pre-manufactured for a large cohort of patients.

The scope of "personalised" medicines is not intended to cover other frameworks such as magistral preparations or the hospital exemption for ATMPs.

The specific technical boundaries of personalised medicine cannot be set in advance and may evolve with the advances in science. Therefore, it is proposed to elaborate this also as part of scientific guidance and to include into the legislation only the concept in an open and broad manner.

It is proposed that the concept of personalised medicines considered the following aspects:

- **Customisation:** Contrary to medicines for which fixed doses are developed, personalised medicinal products will need flexible on-demand doses (customisation). Current legislation requires registration of fixed dosage form strengths in the MA applications or defined adaptations to body weight within a certain range. The same is also true for the composition in terms of excipients and design/shape of the pharmaceutical form. Today's posology per body weight is managed by rounding to the closest available strength. In the future, personalised medicines may require precision, without rounding, as exact adapted dose will be manufactured. This implies flexibility in dosing registration and sufficiently large dosing ranges.
- **Data privacy and digitalisation:** Personalised medicines are closely linked to digitalisation (= digitalised medicinal products or digital therapeutics). There is an anticipated impact on data sharing. So far, only authorised parties, e.g., patients and healthcare professionals have access to the patients' private data, not pharmaceutical industries. A personalised medicine is more than simply personalised treatment, it includes also health platforms for diagnosis and treatment monitoring. This is a global, holistic service with terms and conditions that must be accepted, and which must respect all relevant regulations (data privacy, security).

### **Manufacturing aspects**

It is proposed to make use of the "**platform MA**" concept and its implications on the manufacturing process and Module 3 data requirements as follows:

A marketing authorisation dossier incorporating a platform approach includes a **constant part** and an **adapted part**. Examples of what data may be expected in the constant part are provided below (by use of specific examples, e.g. a viral vector, an adapted monoclonal antibody):

**Constant part:** description of the common elements of the active substance and finished product (e.g. the AAV vector backbone, the mAB core structure), the core manufacturing process incl. process validation, the control strategy and the common set of specifications, starting and raw materials common to all variations of the personalised medicine, equipment and facilities design, excipients common to the personalised medicinal product, container closure system, stability, pharmaceutical development etc.

**Adapted part:** an overview of the adaptations and the range required based on patient criteria and their rationale, the analytical methods to determine patients criteria, starting materials and raw materials specific to the individual patient and their justification, adaptations in the manufacturing process of active substance and finished product and their validation, adaptations in the control strategy necessary, adaptations of excipients, pharmaceutical form, presentation, and/or dose.

Details on the specific data requirements for the constant part and the adapted part are proposed to be elaborated under Annex I technical requirements (Directive 2001/83/EC) (or alternatively in a delegated act) and, if necessary, further specified in scientific guidance (e.g. for the different product classes).

**Lifecycle management of platform:** Lifecycle changes to the dossier Module 3, including its constant (platform-derived) part and its adapted part should be subject to variations in analogy to current practice. Technical data requirements to underpin such variations specific for personalised medicines are proposed to be further elaborated in guidance.

## **2.1. Proposed solutions – in legislation**

A legal framework for personalised medicines is proposed, based on a formal definition of what constitutes a personalised medicine (see also concept paper on core definitions) to be elaborated in more detail in guidance.

The definition of personalised medicine could, for example, be included together with the current definitions provided in Article 1 of Directive 2001/83/EC.

Proposed definition:

*Personalised medicine: a medicinal product whose starting material(s), manufacturing process and/or qualitative and quantitative composition in terms of active substance(s) and/or excipients may be adapted within the parameters defined in the terms of the marketing authorisation to meet specific characteristics of a patient or patient cohort.*

The provisions detailing the specific requirements that would apply to personalised medicines could make reference to an EMA scientific guideline that would describe the limits of accepted adaptations to the core description of the manufacturing process and composition of the medicinal product.

The adaptations, to be included in legislation or scientific guidance, as appropriate, would be limited to/include<sup>4</sup> the following:

- patient specific starting material (e.g. use of patient-derived cells for further manufacturing);
- generic starting/raw materials, but product tailored for patient-specific use (e.g. different protein sequences to target patient or patient cohort-specific antigens, different polymer grades to target patient or patient cohort-specific drug release kinetics, gene therapy with different HLA subtypes) within one indication;
- identical starting material but patient or patient-cohort specific changes to the manufacturing process to manufacture a personalised product (e.g. different layers of API(s) in additive manufacturing to target patient or patient cohort-specific dose);
- identical starting material, same manufacturing process but different composition of the finished product in terms of qualitative and quantitative aspects tailored to an individual patient or patient cohort (e.g. individual strengths or combinations).

The following terms are proposed to be further defined in guidance:

- 'batch' (in the context of personalised medicines, this can be covered under a broad legal definition supplemented with guidance to cover the particularities);
- 'Specific characteristics' can include physiological, genomic or psychological characteristics and are proposed to be further elaborated in guidance.
- 'Patient cohort' it is proposed not to include a fixed number but to define the boundary further in guidance which would allow adaptation as science evolves.

The following adaptations are proposed in the legislation for products meeting the definition of personalised medicine:

- specific requirements for traceability and pharmacovigilance;
- possibility to introduce a range of qualitative and quantitative composition in terms of the active substance(s)/excipients(s) covered in Article 8(3)(c) of Directive 2001/83/EC;

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<sup>4</sup> Further reflection is recommended to decide whether adaptations should be restricted to a defined list (i.e. such as the ones above) or left open, accordingly the wording 'limited to' or 'include' should be selected.

- details in the product information (either in Article 11 or a specific provision dedicated to personalised medicines);
- possibility for alternative manufacturing processes based on sound scientific justifications for each adaptation (reason: in different sections of Directive 2001/83/EC, reference is made to “the manufacturing process” eluding to the need for medicinal products to be manufactured by one process; it may therefore be appropriate to explicitly provide that for personalised medicines the same presentation may be manufactured by different processes);

In this context, it bears noting that a new personalised medicines legal framework may require an update to the concept of New active substance/Global Marketing Authorisation, Article 10 definitions, orphan similarity and the variation regulation.

## **2.2. Proposed solutions – in guidance**

### **Features of personalised medicines**

While we propose that the concept of personalised medicines, which is a novel concept in the EU legislation, is introduced through explicit inclusion in the legislation, a number of specific aspects or technical requirements and application of the concept to the products in development are better addressed in guidance. The reason is that science is fast involving in this area and many aspects can to date not yet be anticipated.

We propose that the following is addressed in guidance:

- For products based on different starting materials, which might lead to a different active substance and therefore a different medicinal product in the current view (e.g. products targeting patient specific mutations), details on parameters classifying a product eligible for personalised medicines and a justification as to why such differences need to be accommodated within one marketing authorisation.
- Differences in patient-derived starting material, which do not render the product a different product under the current legislation but which should nevertheless be described and justified (e.g. autologous cells for cell therapy).
- Technical aspects (and their justification) stemming from the adaptation of the medicinal product to the needs of the individual person (i.e. the patient-tailored aspects (reference is made to the definition above): 1/dose, 2/frequency of administration or administration pattern, 3/drug release kinetics (i.e. through adaptation of the dosage form design/shape or composition in excipients). Guidance should detail manufacturing steps that may be adapted as well as data requirements to justify and support proposed adaptations.
- Traceability of the customised unit dose will be a challenge (concept of on-dose identification/ verification/ tracking), in particular use of barcodes for unique identifier. A shared and connected traceability system between starting/ raw/ intermediate material manufacturers and end users (e.g. hospital pharmacies, individual patients) is foreseen that should be covered by guidance.

### **Manufacturing aspects**

The start and end of the manufacturing process of a personalised medicine/active substance needs to be defined as for every medicinal product. The proposal is that the same principles as for other medicinal products apply with some considerations for starting materials, start of manufacturing under GMP (i.e. arrival of the starting materials at the manufacturing site) and process end with the release by the QP. These additional considerations should be addressed in scientific guidance.

The production of the medicinal product upon patient request could be finalized either at the registered manufacturing site(s), in a pharmacy setting, compounding/community setting, or even in the patient’s home. This would challenge conventional pharmaceutical supply chains and the regulatory framework. For example, in certain scenarios a sharing of responsibility (authorisations) and a shift of final quality control from the pharmaceutical industry to treatment centres/patients would need to be embedded into a framework. A set of guidance/rules to ensure that the medicinal product is not negatively impacted by this process and consistency across several sites can be ensured, is proposed to complement the new provisions (*reference is also made to CP5 on Core definitions*).

- **GMP principles:** Specific adaptations of GMP principles to personalised medicines, if required, should be considered as part of guidance but not as part of legislation. GMP principles should apply to personalised medicines as they apply to non-personalised medicines.

- **Batch definition and batch release :** Since volume of production will be calculated based on actual patients' demand (instead of mass production based on expected product consumption), an impact on the batch definition is anticipated. It is suggested to keep the definition of batch sufficiently broad and to accommodate specificities resulting from personalised medicines through guidance as there is a need for adaptations as science evolves. One consideration is to define a batch through a constant part in the input and starting materials. The batch must be released/certified as conform to the constant and the adapted part as described in the MA. A general batch definition is proposed at the start of this paper
- **Software and equipment:** As part of personalised medicine, innovative techniques may be implemented such as additive manufacturing techniques that require specific equipment (e.g. printers) and software. We can foresee situations where equipment design governs the control strategy. Consideration should be given to what is to be covered in Module 3 and what will fall under the PQS (reference is also made to Continuous Manufacturing/Innovative manufacturing methods and Pharma 4.0).
- **Data requirements for platform:** Specific data requirements to describe the platform used, which includes a constant part of the product and data and an adapted part to the individual patient or patient cohort.
- **Lifecycle changes:** A procedure to manage updates and the lifecycle of personalised medicines. Here we propose that the variation framework is adapted to incorporate lifecycle changes to the personalised medicine.

### **Clinical trial design**

Clinical trials design will be a challenge as all personalised medicine "configurations" can likely not be tested prior to marketing authorization. Therefore clinical data sets are expected to be substantiated by real life data collection.

## **3. Continuous manufacturing/innovative manufacturing methods**

### **Problem statement**

#### **Continuous manufacturing (CM)**

In recent years CM has gained attraction as a solution to the increasing pressure on drug manufacturers to reduce development time and costs, and to assure robust supply of quality product (through enhanced process control strategies). Five Marketing Authorisation Applications and one variation using this technology have been submitted, all of which have been approved. Currently, although applications for all possible modalities as describe in section 2.1 of the draft ICH Q13 guideline have not yet been received, no regulatory barrier in current legislation has been identified for the registration of this technology.

However, there are a few regulatory concepts based on the batch-mode of manufacture which may require consideration to fully embrace CM into the EU regulatory framework. These are:

**Batch concept:** Although the concept was originally developed for batch processes, it is being applied for CM for regulatory purposes since material needs to be disposed and traced in a discrete manner (e.g. even if product is manufactured in a continuous manner, material is handled and distributed in a discrete operation). However, it is acknowledged that there are subtle differences between batch and continuous processes, e.g. in CM there can be greater flexibility of the input/output material quantities, dependent on the run time required to execute a manufacturing order.

Since processing times can have an impact on process performance e.g. fouling, heat up, in EU applicants are requested to describe the proposed commercial batch size or range in the dossier (e.g. based on run time, quantity of output material, etc), as for batch processes, in line with current NtA. This proposal is included in the published ICH Q13 draft (see sections 2.2. and 4.3).

However, the batch concept and its definition was a topic heavily discussed with industry during the ICH Q13 drafting process and may come up again as part of its public consultation. We need to monitor and evaluate whether additional information is brought to our attention that supports further discussion on this topic and reconsideration of the current EU position (described in the paragraph above). The Agency will engage again with the EC if this happens.

- in the case of **end-to end CM**, manufacturing approach in which active substance and finished product unit operations are integrated across the boundary between active substance and finished product to form a single CM process (i.e., the active substance is continuously formed and processed through integrated unit operations to result in the final finished product), special considerations would apply. To note, in this CM mode, the active substance may be or may not be completely synthesized when excipient addition starts.
  - Consideration should be given to the impact of this approach on current GMP requirements. From a practical perspective, it is likely that the active substance portion will fall under GMP for finished product because it could entail addition of excipient(s) before the active substance synthesis is completed. Revision of the legislation may be required to clarify these GMP requirements.
  - The ICH Q13 draft document requires applicants to establish an active substance specification, thereby defining the quality of the active substance and facilitating the management of lifecycle activities, investigations, development of pharmacopoeial monographs, etc. Since the active substance is not routinely tested, the finished product specification will include attributes typically associated with the active substance quality (active substance impurities, residual solvents etc.), as appropriate. This is currently described in Annex IV of ICH Q13 draft and may require an adaptation in NtA, but no change in the legislation is currently deemed necessary. This point has been brought to the attention of ICH M4Q colleagues.

**Digitalization and modelling.** CM is associated with enhanced control strategies where system design, as well as Process Analytical Technologies (PAT), advanced control systems and modelling monitor the process and guarantee the system operates in a state of control. This may not require an adaptation of the legislation, but to assessment considerations. However, these concepts are not only applicable to CM, and this broad area merits guidance of its own. For further discussion on this topic, please refer to the section on Pharma 4.0.

**Control strategy:** we can foresee a situation where equipment design governs the control strategy. Consideration should be given to what is to be covered in Module 3 and what under the PQS (refer to pharma 4.0 section).

**Product composition:** according to current EU legislation, a product presentation/strength must have a unique composition, and there is no scope for alternative compositions. In the future, the use of different compositions for a single strength of a medicinal product will be probable, as a consequence of the implementation of alternative manufacturing modes within the same MA, for example batch and CM processes; thus, EU legislation should accommodate this possibility. Acceptable justifications and extent of composition variability should be covered by guidance and NtA. This may also apply to other innovative technologies, particularly personalised medicines.

**GMP:** CM is well suited to miniaturisation and hence decentralised manufacture (e.g. via portable manufacturing facilities). It needs to be considered whether any change on current GMP and assessment practices are to be made to accommodate these type of approaches (see discussion below under innovative manufacturing technologies and section on decentralized manufacture).

### **Innovative manufacturing technologies**

#### **Additive manufacturing (e.g. 3D printing).**

Additive manufacturing is the general term for those technologies that, based on a geometrical representation, create physical objects by successive addition of material. Considering the likely range of technologies and their complexity, expected applications are of smaller scale (e.g. personalised manufacturing, POC and hospital/pharmacy), although larger scale manufacturing is not excluded. Therefore, adoption of this technology may be one of the drivers for the implementation of

decentralized manufacturing for medicines and medical devices, as well as Pharma 4.0. It is foreseen that this technology could use MAH supplied manufacturing platforms, such as 3D printers.

There are several generic steps in additive manufacturing: **pre-processing** (e.g. system design,), **manufacture** (e.g. printing), **post-processing** (e.g. cleaning,) and **testing** (e.g. quality control). Conceptually, and from a high-level overview perspective, these process steps are similar in scope to those of traditional, centralised manufacturing; however, in practice, they are markedly different and additive manufacturing technologies can fit under the decentralised manufacturing paradigm, with all its associated considerations (see section on decentralised manufacturing).

Additive manufacturing offers new opportunities which, at the same time, raise specific issues which should be addressed through specific guidance, e.g.:

- variability in dosage form composition, structure and shape (see section on Personalised medicines)
- batch definition and disposition
- validation and control strategy
- suitability of current compendial tests, pharmaceutical technical procedures and standard terms
- supply and receipt of raw materials, starting materials, equipment, etc.
- data integrity, storage and review
- batch release, including real-time release testing (RTRT)-stability

**Advanced process control and automation.** Important advancements are being made in the area of process control and automation including sensor technology, data analytics and system modelling, and manufacturers will increasingly rely on these innovations to design, understand, and monitor processes. The combined capabilities of various sensors will create an unprecedented ability to measure and control process variables and product attributes. Sophisticated analytics, models, and artificial intelligence will likely be required to support advanced process-control strategies, continuous process verification and ultimately real-time process optimization, and automated operation and management of manufacturing (see section on Pharma 4.0).

**GMP:** As indicated in the CM section above, decentralised manufacturing at different locations or even at the point of care presents an opportunity to redefine the concept of a manufacturing facility, impacting the global supply chain and offering the possibility of creating integrated, flexible, and distributed manufacturing networks. These modular systems can be easily replicated and deployed quickly in an existing facility or to other locations and thus provide the ability to respond rapidly to patient and health-care system needs that range from personalized therapies to varying patient needs across geographic and demographic boundaries. It is important to note that integrated, flexible, and distributed manufacturing networks will be extremely difficult to achieve through traditional quality-management systems that were built around large, centralised facilities and associated supply-chains. The ability to achieve consistency of operations and quality in smaller, more modularized operations will depend heavily on integrated advanced process control and automation and, the use of platform technologies. It needs to be considered whether any change on current GMP practices are to be made to accommodate these type of approaches (see section on decentralised manufacturing).

### **Process platform technologies**

Platform processes have a number of advantages over the development of a bespoke process for each new product and are being developed in the frame of innovative technologies (see the Concept Paper on core definitions). Process platforms can cover dosage form design, digital development and intelligent production of the entire line. They may be used more widely in the future under several modalities (e.g. proprietary to the MAH or not, one MA or different MAs). Since this is a novel concept, further internal reflection is needed and it is not possible to make a recommendation at this stage.

### **Nanomedicines**

Although some nanomedicines have been registered in Europe, these are limited and mainly consist of liposomal formulations. Only recently lipid nanoparticles for siRNA and mRNA delivery (COVID19 vaccines) have been introduced into the EU market. This is an emerging field which can offer many possibilities to deliver therapeutics to achieve drug targeting, controlled release and/or improved transport across biological barriers, but its full potential remains to be exploited.



One of the main challenges associated with nanomedicines is that this product class covers a wide variety of materials and structures (e.g. liposomes, lipid nanoparticles, polymeric nanoparticles, iron nanoparticles, nanocrystals, dendrimers, etc) each of them with its own particularities. Characterisation and analytical tools are not yet standardised, and the link between the manufacturing process, quality characteristics and product performance is not always elucidated in full, which poses a challenge for developers (innovators and generics) and regulators. This, per se, does not require a change in legislation, but further research from the scientific community to address the gaps in knowledge and support the registration of these products.

### **3.1. Proposed solutions – in legislation**

#### **Continuous manufacturing:**

As indicated above the following is to be considered:

- Reflection may be needed, after the consultation with stakeholders, on whether to maintain the **'batch' concept** for CM.

In this regard, it is worth noting that as part of ICH Q13 discussions some industry stakeholders have been advocating that because of the continuous flow of material it is not scientifically justified to use the concept of batch, segregating material into discrete amounts, for CM. However, the current EU regulators view is that the concept should be maintained for regulatory purposes to handle material traceability and disposition. This is the current position in the published draft ICHQ13, but we envisage that the discussion may be reopened if additional comments on this regard are received as part of ICH Q13 Step 2 consultation which is currently on-going. If additional information is brought to our attention that supports further discussion on this topic and reconsideration of the current EU position, the Agency will engage again with the EC.

#### **Innovative manufacturing approaches**

- An aspect to consider in the context of innovation and modernised control strategies would be the acceptability of having **flexible product compositions**. This may be considered in the context of personalised medicines, but also for example in the case of developing CM process for products traditionally manufactured by a batch-process. For example, in those cases there may be the need to make some changes in the product composition to enable continuous processing. If the applicant intends to maintain the batch and the CM processes, this may lead to the same product with alternative compositions on the market. Consideration should be given on whether current legislation allow for this scenario.
- It is also important to consider that future innovative technologies/modernised control strategies may require **revision of the categories in the variation classification guideline**. Changes may be required to introduce some scopes or revise some of the existing scopes to allow (real time) changes in adaptive manufacturing processes and/or control strategies without the need of constant regulatory oversight, when supported by appropriate data.
- Process platform technologies: there should be clear distinction between what constitutes a process platform technology, and what the expectations are in that regard (please see Concept Paper on core definitions).

### **3.2. Proposed solutions – in guidance**

#### **Continuous manufacturing:**

It is proposed to use ICH Q13 as much as possible and only develop or update existing EU guidance if any aspect needs further guidance at EU level.

As mentioned earlier, for end-to-end CM dossiers, since there is no boundary between active substance and finished product, adaptation of the CTD structure/Notice to Applicants volume 2B should be considered (i.e. boundary between 3.2.S and 3.2.P). This aspect has been discussed at the level of ICH Q13 EWG and some information has been included in Annex IV of the guideline. It has also been highlighted to ICH M4Q EWG.

In terms of GMP, revision of relevant guidance may be required to clarify GMP requirements for end-to-end CM processes.

### **Innovative manufacturing technologies:**

For **additive manufacturing** it is proposed that guidance is developed to cover aspects related to:

- variability in dosage form composition, structure and shape,
- batch definition and disposition,
- validation and control strategy,
- suitability of current compendial tests, pharmaceutical technical procedures and standard terms,
- supply and receipt of raw materials, starting materials, equipment, etc.,
- data integrity, storage and review,
- real-time release testing,
- stability.

As indicated above, guidance may need to be developed to describe how to handle **flexible product compositions within a MA**, not only in the context of personalised medicines, but also for example in the case of developing CM process for products traditionally manufactured by a batch-process. For example, in those cases there may be the need to make some changes in the product composition to enable continuous processing. If the applicant intends to maintain the batch and the CM processes, this may lead to the same product with alternative compositions on the market. Consideration should be given on how to handle this in 3.2.P.1. and the product information.

As indicated above, consideration should be given to the development of guidance on **data analytics**, including **modelling** (EU specific or at ICH level) and on batch definition.

In addition, with future innovative technologies/modernized control strategies, including CM but not only, **performance-based process monitoring** may become more frequent. It should be considered whether changes in NtA volume 2B are needed to accommodate these approaches (see section on Pharma 4.0).

With regards to nanomedicines, several regulatory guidelines are available in EU<sup>5</sup>, however as described above, the experience is still limited and further research and exposure is required to develop further guidance.

Finally, it is recommended to also consider whether specific guidance around platform technologies and associated regulatory expectations.

## **4. Impact of Pharma 4.0 on manufacturing**

Faster mobile communication (5G), the Internet of Things (IoT), artificial intelligence (AI), robotics, blockchain, virtual and augmented reality (VR, AR), and cyber physical systems are some of the technologies that currently drive what has been termed "the 4<sup>th</sup> industrial revolution" (Industry 4.0).

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<sup>5</sup> [Multidisciplinary: nanomedicines | European Medicines Agency \(europa.eu\)](#)

Large amounts of data are generated, validated, stored, and analysed by advanced data analytical tools for predicting, modelling, controlling, and trending. The vision of future production contains platform and modular manufacturing systems and foresees scenarios in which medicinal products can control their own manufacturing process and in which machines and devices are communicating, continuously and in real-time. "Pharma 4.0" is a holistic operating model for pharmaceutical factories and supply chains of the future based on Industry 4.0 capabilities, digital maturity, and data integrity. It is by design<sup>6</sup>, a framework for adopting digital strategies in pharmaceutical industries.

Pharma 4.0 represents a shift away from focusing on production using fixed process parameter settings by using a system of real-time monitoring, simulation and self-control. The goal is to enable processes to self-adjust based on data from interconnected systems, not only to ensure the product meets its predefined specifications, but also to reduce quality-defects. This concept builds on the established principles of quality by design (QbD) and process analytical technology (PAT) described in ICH guidelines.

While certain applications can be implemented and used without any regulatory restriction, some applications may require regulatory visibility and hence signal the need to assist industry in the implementation of this concept. There is a general need, not just linked to Pharma 4.0, to update the current legal and guidelines framework to reflect current expectations in relation to control strategy (refer to the general remarks of the overall concept paper)

It is an evolving field, and a further deeper reflection will be needed on how the legislation should be changed aligning it with the commitments expressed in the 2018 Coordinated Plan on AI<sup>7</sup> and the actions outlined in the 2021 review of the Coordinated Plan<sup>8</sup>, Fostering a European approach to Artificial Intelligence.

In June 2021 EFPIA member companies submitted a published paper to the GMDP IWG identifying the following key areas of importance to industry<sup>9</sup>

- Augmented Reality in Manufacturing,
- Use of chemometrics, and adaptive process models; use of integrated manufacturing systems on a local and/or site-wide scale,
- Automated and standardized manufacturing processes,
- Interpretation of stability data,
- QA/QC (especially QP release) - use of artificial intelligence and 'at time' release,
- Automated and standardized review processes internally and externally with multiple Agencies,
- Use of robotics.

The current EU legislation requires manufacturers to regularly review their manufacturing methods in the light of scientific progress and submit any necessary variations; although no specific barriers in current legislation were identified in the EFPIA paper, some recommendations to revise or update current GMP guidance were proposed. It is also important not to overregulate this field as this would not only burden both the industry and the competent authorities, but would also slow down innovation and patient access to innovative and affordable medicines.

The importance of Pharma 4.0 is that there will be a shift from primary control being exerted via the finished product specification to a control strategy that consists of a unique 'multi-dimensional' specification meeting the overall target product profile, adjusted in real-time, and taking into account the self-learning or self-adaptation of the manufacturing system. Furthermore, an additional factor influencing the change in focus is the shift from the "product is the process" approach to product adaption based on increased process/product knowledge and understanding. Further reflection on whether this can be accommodated through the design space concept is needed.

Based on the above, how best to adapt the EU variations regulation, lifecycle change management practices and the way inspections are carried out in this new paradigm should be decided. The new paradigm will facilitate and align with the implementation of ICH Q12 tools and the need for closer

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<sup>6</sup> [Pharma 4.0™: Hype or Reality? | Pharmaceutical Engineering \(ispe.org\)](#)

<sup>7</sup> European Commission Communication Coordinated Plan on Artificial Intelligence (COM(2018) 795 final)

<sup>8</sup> European Commission Communication Fostering a European approach to Artificial Intelligence COM (2021) 205 (final)

<sup>9</sup> [EFPIA MQEG Digitalization Discussion Paper](#)

collaboration between assessment and inspection functions. For example, evaluating the claimed Established Conditions for an instrumented, self-adjusting process would require careful consideration of both the content of the Module 3 (M3 quality) of the eCTD and of the manufacturer's Pharmaceutical Quality System (PQS) effectiveness. Regulators will need to ensure that, as digitalisation of manufacturing progresses, appropriate controls remain in place to maintain adequate oversight of activities (via GMP-PQS and/or via M3 of the eCTD). This is particularly germane during the assessment phase of a product lifecycle. An illustration of a possible integrated manufacturing system, utilising 'internet of things' devices and sensors to measure process specific variables, and integrating them with variables from other manufacturing systems to exert control over the process, is illustrated in Annex 1.

The control strategy of a self-learning manufacturing system (under Pharma 4.0) will likely be reliant on the real-time collection and interpretation of large amounts of data by innovative systems, such as "Software as a Service" (SaaS), cloud-based services, artificial intelligence (AI) systems (including machine learning (ML) algorithms) and Blockchain. These systems can directly impact the quality of the output material, and they will be frequently updated during the life-cycle of a product. The relevant level of information on Pharma 4.0 manufacturing systems should be included in the submission (in the context of the development and definition of the overall control strategy) and maintained throughout the lifecycle of the medicinal product. The data analysed by these systems may be inspected and/or requested during assessment.

Similarly, implementation of Pharma 4.0 hardware solutions, such as high performance computing and robotics, and instrumented equipment trains, will also require regulatory visibility through the lifecycle of the product.

A good opportunity for EU to lead on the subject of Pharma 4.0 at an international level is through ICH and PIC/s, to focus on defining and setting common expectations with respect to pharmaceutical regulation.

#### **4.1. Proposed solutions – in legislation**

It should become possible to proactively interact with applicant/MAH, e.g. raise *ad hoc* clarifications, and receive solicited responses, during the review process, whilst still maintaining the current assessment cycle.

#### **4.2. Proposed solutions – in guidance**

Implementing Pharma 4.0 based manufacturing concepts could require alignments of expectations and definitions with other parts of the legal framework that deal with digitalisation (e.g. artificial intelligence) such that it does not create a divergence.

New Pharma 4.0 definitions and terminology associated with the technology (such as augmented reality) and also wider identification of parameters that are part of the overall control strategy, for example critical equipment attributes, critical software attributes, critical model attributes, etc..

3. Update of GMP chapters and annexes to provide further guidance on:

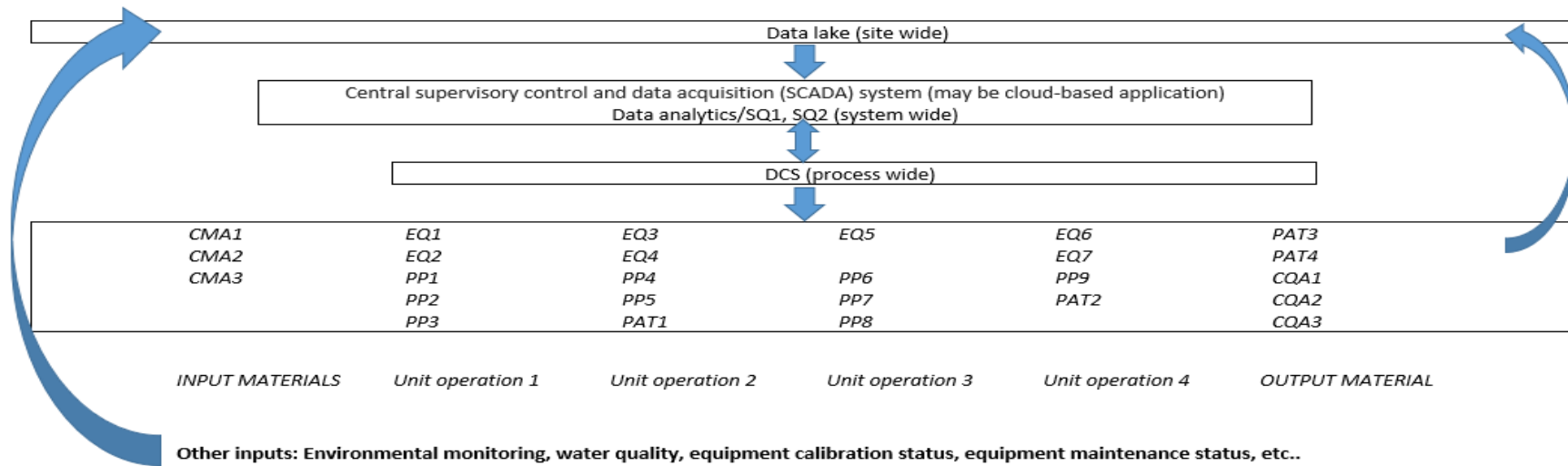
- The use of adaptive models to support e.g. real time release, continuous processing, generation of process understanding, or investigations.
- The use of automated real time release, which is supported by an artificial intelligence analysis of related deviations and changes, as well as fully automated control of supply.
- The qualification and validation of self-learning robotic systems.
- How data integrity can be established and maintained
- Risk based approaches to the qualification of suppliers of services that support the implementation of Pharma 4.0, including IT infrastructure and cybersecurity.
- The acceptable performance criteria or controls for Automated and Standardized Review Processes.

4. Update of Network and EMA Guidance to introduce Pharma 4.0 terminology, concepts and processes and to reflect the shift from eCTD to GMP. For example:

- Update to the Notice to Applicants to reflect how dossier requirements would need to be adapted for guidance on submission of the overall control strategy (including those relying on Pharma 4.0) in a defined section of M3 of the eCTD and the summarised data but also guidance on reviewing the data submitted to authorities. This should link to Q12 product life-cycle management concept.
  - Manufacture of the Dosage Form, because elements of Pharma 4.0 may be used in a supportive or direct manner during development/routine manufacturing and overall control strategy for output materials.
  - Consider update to EMA IMP guidance, to specifically call out expectations regarding elements of Pharma 4.0 that relate to the overall control strategy for IMPs.
  - Revision of EMA guideline on Process Validation, to highlight link between data analytics/digital control strategies with on-going process validation.
  - Update of Variations guideline to include selected aspects of Pharma 4.0, e.g. use of/intention of real-time adaptive models in a control strategy, and adjustments in overall control strategy as a result of real-time control and analysis of manufacturing system.
5. ICH Guidance. For example,
- Revision of ICH Q8/ICHQ8-Q10 to further consider how best to define models (there is some ambiguity in assignment of impact, and of what constitutes a model). Given that, e.g. VR/AR/ML may form part of the development of a product, recognition that such information should form part of S.2.6/P.2.3. Inclusion of further granularity regarding critical aspects of manufacturing systems (e.g. critical equipment parameters, critical software parameters, etc.) and their location in M3.
  - Preparation of an ICH Guideline on Data Analytics (digital control strategies). Furthermore, perhaps an ICH series on digitalisation may be appropriate, dealing with different themes, such as clinical real-world evidence, digital technologies used with medicinal products, data analytics, etc.
6. Update of inspection and assessment practices.
- There will be a need to reflect further on the inter-play between inspection and assessment on applications based on Pharma 4.0 concepts. There will be an increase of pre-approval inspections (by both inspectors and assessors) to cover elements of the control strategy that may not be in the dossier, in order to build confidence on the validity of data submitted and understand how it has been used by the applicant to construct and demonstrate the overall control strategy.
  - Introduce a hybrid inspection concept into the Compilation of Union procedures for dealing with Pharma 4.0 applications: e.g. distant assessment by inspectors and assessors, and then further evaluation in the field

**Annex 1: Example of a potential INTEGRATED (INSTRUMENTED) MANUFACTURING SYSTEM**

- |     |   |     |   |
|-----|---|-----|---|
| PP  | (Critical) Process parameter (e.g. speed, pH)       | EQ  | (Critical) Equipment parameter (e.g. resistance in a pump, equipment design)  |
| MA  | (Critical) Material attribute (e.g. zeta potential) | SQ  | (Critical) Software parameter (e.g. process specific model, bespoke software) |
| QA  | (Critical) Quality attribute (e.g. assay)           | PAT | (Critical) Process Analytical Technology (e.g. chemometric application)       |
| DCS | Distributive Control System (or similar system)     |     |   |



## 05. Concept paper on **Core definitions**

**Main theme:** Technical input for considering the continued suitability of existing definitions that relate to the understanding of medicinal product and its characteristics. Scope [Dir 2001/83/EC](#) and [Reg \(EC\) 726/2004/EC](#)

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic lead	Experts from EMA
Drafting group	Experts from BWP, QWP, CAT, CHMP, CMDh, IWG, HMA/CMDh Innovation Network Borderline Coordination Group, VWP (via written consultation), EMA and additional experts from AEMPS, PEI and ANSM.

Note: In this concept paper, proposed modifications to existing definitions are shown as:

~~Strikethrough~~ – proposed deletion

**Bold, underline** – proposed additional text

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# 1. Extended definition of medicinal product

## 1.1. Rationale for considering a change

- Consideration for changes in the definition of a medicinal product (MP) and/or substance has been given to address products that have challenged the current definition of a 'MP' or 'substance' during borderline discussions and/or court cases:
  - Contraceptives and abortifacients since conception is not a disease.
  - MP/device combination medicinal products, including those involving software, complex products where the "device" may have to be considered part of the active substance or those involving components from various framework.

Note: Manufacturing devices used to produce biological MP/devices would not be considered as combined products unless the device would remain part of the MP (e.g. radionuclide generators).

- The definition of MP refers to substances or combination of substances reflecting on traditional forms of MPs; however, an increasing number of MPs may be coupled with medical devices (MD), software, other components not covered under the pharmaceutical legislation such as artificial intelligence (AI). Already, novel MP/device combination products and interface with the Medical Device Regulation (MDR)/In vitro Diagnostic Regulation (IVDR) have challenged the approaches to accountabilities, created duplication of requirements or gaps; this has highlighted the need for integrated pathways – both at time of development and regulatory assessment - to bring together relevant stakeholders involved in the development and supervision of novel combined products (as defined in Section 1.2) and regulated under different regulatory frameworks, e.g. medicines regulators, notified bodies (NBs) and device regulators.
  - Changes ought to be introduced to clarify the marketing authorisation holder (MAH) responsibilities in the oversight of such combined products (e.g. medicinal products combined with device/AI/connected software at point of care manufacture, during administration and/or for clinical use (including for convenience tools) as well as the relevant framework/requirement applying to software applications and device transmitting information to the software.
  - There may be an overlap between the scope of the MP benefit-risk assessment and that of the other framework. In that regard, as an example it should be clarified that the scope of the regulatory review will also consider the impact of any digital health application on the B-R assessment of the MP, as well as the risk-based approach taken by the applicant to handle this impact (e.g. risk of medication errors).
- The applications of artificial intelligence are expanding in medicine, for example, in areas such as manufacturing, diagnostics, clinical trial design, and pharmacovigilance, amongst others. EMA's enlarged role in medical devices and companion diagnostic consultation procedures, and in the coordination of expert panels will also increase the agency's exposure to AI (Reinforced role (2020/725), MDR (2017/745) and the IVDR (2017/746)).
- For the legislation to be future proof, changes should be agnostic of technologies but focus on ensuring clear ownership of the interpretation and application of the definition.

## 1.2. Proposed solutions – in legislation

- Whilst **no change to the definition of medicinal product is proposed**, the Commission may consider strengthening Art 2(2) to clearly put the onus on applicants to demonstrate whether or not a given product would be expected to have an action consistent with the second part of the definition of a medicinal product where doubt exists. This is in view of previous and ongoing court cases where competent authorities have been asked to provide evidence of such effects to support classification as a medicinal product in cases of doubt<sup>1</sup>. There was also a proposal to add “with a medical purpose” in the definition of the MP in line with the definition of MDs although this was not endorsed by the drafting group as it would restrict the scope of the concept of medicinal product. The definition was modified in the past to disconnect from this notion and refer more generally to “with a view to restoring, correcting or modifying physiological functions” – such broadening encompasses for instance contraceptive pills that are not intended for a medical purpose.
- **Revise the description of a substance by introducing micro-organisms (incl. yeast) and fungi** as separate entities under the substance definition whilst ensuring consistency across various definitions (e.g. herbal substances refer to fungi).

### 3. Substance:

Any matter irrespective of origin which may be:

— human, e.g. human blood, secretion, and human blood products;

— animal, e.g. ~~micro-organisms~~, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

— ~~vegetable~~ vegetal, e.g. ~~micro-organisms~~, plants, parts of plants, vegetable secretions, extracts;

— chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis,

- micro-organisms, including yeast

- fungi<sup>2</sup>.

- **Consider clarifying that the definition of a medicinal product also encompasses products for the control or support of conception (as in the Medical Device Regulation) and can be used in combination with components from other frameworks** which would trigger some common oversight per next proposal.

### 2. Medicinal product:

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<sup>1</sup> According to the present definition of medicinal product and interpretations of the Court of Justice of the European Union, the criteria for classification of a product as a medicinal product by function is based on a case-by-case assessment of, inter alia, that product’s specific pharmacological, immunological or metabolic properties, to the extent to which they can be established in the present state of scientific knowledge, and the immediate or long term beneficial effect produced by the product. In several cases, national courts have demanded very high level on scientific evidence for a classification and the lack of precision in the criteria for classification is challenging for both companies and national authorities. From a purely scientific perspective, data on the specific product or studies on bioequivalence is needed to be able to assess the effect of a specific product on a high scientific level. For a product not put on the market as a medicinal product, these data is almost never available. From a public health perspective, it is not reasonable to demand a study battery on par with a market authorisation application for an assessment if the product is a medicinal product by function. Some extrapolation needs to be tolerated or only authorised medicines would be included in the definition. There are also big challenges with substances with dual functions, or claimed dual functions, with both beneficial and non-beneficial effects. For products with a single active substance the medicinal properties of the product should have precedence. An interpretation in connection with these aspects is expected from the Court of Justice in the case C-616/20, but a clarification from the legislators, by legislation or guideline, would be a better solution.

<sup>2</sup> <sup>2</sup>Title 1 definitions; Herbal substances: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh.

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

**Notes:**

**This definition encompasses products for the control or support of conception.**

**Medicinal products can in addition include or interact with one or several medical devices, software or other components regulated under different framework. See combined products.**

- The definition of a MP utilises the concept of "exerting a pharmacological, immunological or metabolic action" which are concepts for which the Agency and its scientific committees, both CAT and CHMP have been consulted in the past - under Article 57(p) of Reg (EC) No. 726/2004 – and are currently addressed in MEDDEV guidelines; in view of their importance in the determination whether the product at stake is a MP, **the Commission should consider whether a legal definition for these terms (pharmacological, immunological or metabolic action) or a legal basis for implemented texts** should be introduced in the Pharmaceutical legislation. In addition, the Commission might consider clarifying in supporting guidance, such as the Notice to applicants that the burden of proof remains with the applicant especially in relation to the first indent of the MP – if they consider their product should not be classified as a MP.
- **Introduce an integrated development and evaluation pathway under the Pharma legislative framework** to facilitate the development, assessment and oversight of medicinal products "to be used" with components regulated under different frameworks, such as medical devices, including software, artificial intelligence etc. materialised **by 1) introducing a definition of "combined products"** encompassing combination of at least 1 MP and at least one additional component covered under a different legal framework than the pharmaceutical legislation<sup>3</sup> but necessary for the MP to exert its properties and claims, e.g. MP+MD, MP+ Blood Tissue Cell component (BTC), MP + IVD or companion diagnostic (CDx); **2) by adding a statement next to the MP definition that it can also interact with relevant components governed under different frameworks such as MDs 3) referring to an integrated pathway** with an option for the Agency/NCAs to initiate a consultation process with other assessment bodies from the other framework similarly to what has been introduced by the IVDR especially when such interaction may affect the benefit/risk for the patient. This proposal is not intended to replace existing measures introduced as part of the MDR (such as Article 117 of the MDR) but is complementary; such consultation is optional and should follow a risk-based approach, and only be initiated where needed for example in situations where the interlinks between the two frameworks may be limited (e.g. co-packaged or separately packed). It is not proposed to encompass situations where the MP/substance is ancillary to the MD, nor those situations where the other component is not intended to or expected to affect the efficacy/safety of the MP.

*A "combined" product<sup>4</sup> can be 1) a product comprised of one medicinal product (MP) and one or more other components regulated under different frameworks, i.e., MP/MD or MP/ATMP/MD,*

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<sup>3</sup> This definition does not encompass combination of 2 MPs, including combined ATMP.

<sup>4</sup> The proposed term may require further reflection; the drafting group also discussed the term "combination product" or "combined medicinal product" but there was some concern that this may be confused with fixed dose combinations/combination packs and/or imply that the whole product is governed under the MP framework which is not the intent here. For example, the Questions & Answers for applicants, marketing authorisation holders of medicinal products

*MP/BTC, MP/IVD that are physically, or otherwise combined or mixed and produced as a single entity [aka as integral] and/or packaged together in a single package for administration/use ; 2) a MP intended for use with another component made available separately and regulated under a different framework (MDR, IVDR) .*

- **Introduction of a legal basis for expanding the role of EMA/national competent authorities in the review of these combined products by enabling possible consultation with other relevant stakeholders** according to a risk-based approach– at time of development and registration - within **one integrated pathway** with the process similar to what is foreseen for companion diagnostics, e.g. by amending REG 726/2004 Art 57 1) to incorporate combined products “ a) *coordination of the scientific evaluation of the quality, safety and efficacy of medicinal products and combined products which are subject to Union marketing authorisation procedures;*” May need to provide additional flexibility to the current scope defined by Article 2, e.g. “for the purpose of paragraph 1 of this Article, the Commission may, by means of implementing acts, adopt decisions on whether a specific product or group of products is to be considered as a human medicinal product under that Directive. ”

Note: It is not proposed to overrule the current measures in place in the context of MDR/IVDR but instead to provide additional options mostly for situations where the combined products do not fall under these “integrated” frameworks.

- **Clarify the oversight role of the MAH on the safe and effective use of combined products,** MP used in combination with and/or connected with other constituents such as medical devices, including software, etc for example under Article 6 1a) of the Directive.
- **Expand the scope of scientific advice (SA) (under Article 57, 1 (n) of Reg 726/2004) to encompass combined products interacting with components governed under other frameworks whilst ensuring the possibility to call for experts/representatives from the other regulatory bodies (e.g. notified bodies) and introduce or strengthen the legal basis for technology focused scientific advice/qualification e.g. (n) *advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products and combined products in cooperation with*;**

Note: This approach should also be possible when seeking national advice at MS level, or regardless of the path used or to be developed in the future.

- **Introduce a definition of “fixed (dose) combination” and “combination pack”** in the legislation – currently referred to in Article 10b of Directive 2001/83/EC and Chapter 1 section 5.5. of the Notice to Applicant.

*Fixed (dose) combination: Combination of active substances within a single pharmaceutical form.*

*Combination pack: A combination package is a package that contains more than one medicinal product placed on the market under a single tradename or intended to be used in a medical treatment where the individual medicinal products are for medical purposes simultaneously or sequentially administered. The placing on the market of more than one medicinal product as a combination pack must only be considered in exceptional circumstances when it can be*

*demonstrated that it is justified based on public health reasons.*

Note: Fixed combinations as defined above or packs comprising 2 or more medicinal products (including ATMPs) co-packaged for public health reasons (aka as combination pack) are not considered per se a combined product unless they fulfilled in addition the criteria above of mixing components from different frameworks.

### **1.3. Proposed solutions – in guidance**

- Development of lean processes and data requirements guidance for applicants and regulators in the context of an integrated pathway for the provision of advice and assessment of combined products and future complex combinations (e.g. PGWP concept paper)
  - E.g. Molecule-Independent Clinical Device Bridging Approach where Company proposes an on-body delivery system (OBDS) platforms for monoclonal antibodies (mAbs); this not only about device performance for the CE marking but also data for the purpose of the MAA (irrespective of the configuration i.e. device integral, co-packaged, referenced in the product information (PI) that are needed by medicines regulators to ensure the safety and performance of the medical device when used in combination with the medicinal product has no negative impact on Quality, Safety, Efficacy of the MP.
- Creation of risk-categorisation principles for combined products and development of guidance/Q&A by the Agency in collaboration with appropriate stakeholders regarding the development of combined products including further complex combinations (such as medicines which have digital systems that are convenience tools associated with their use), fostering a risk-based approach and appropriate links with existing framework associated with AI, including for example health-care professional decision making facilitated by AI/software<sup>5 6</sup>.
- Development of technical guidance relating to the possibility to re-use data for the assessment of platform medical devices for use with different medicinal products.
- Criteria for acceptability for combination packs for public health reasons should be clearly established in the notice to applicant or other implementing guidance to avoid the misuse of the concept for convenience and commercial purposes.

### **1.4. Additional considerations**

- The creation of a single/integrated pathway for all types of combined products is proposed also for national approved products and may equally be challenging at national level leading to potential delays during assessment.
- [Under ASMF concept]: Consider possibility of exchanging information between third party (e.g. device, software) producers and regulators (impacts both development & MAA) depending on the scope of the master file concept.

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<sup>5</sup> AI Regulation: [https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12527-Artificial-intelligence-ethical-and-legal-requirements\\_en](https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12527-Artificial-intelligence-ethical-and-legal-requirements_en)

<sup>6</sup> Machine learning enabled medical devices: <http://www.imdrf.org/consultations/consultations.asp>

- [Under inspection framework]: Consider introducing the ability to expand scope of inspection to manufacturers of components used in combined products (e.g. device/software) following convergent development to enhance regulatory oversight of convergent developments.
- Potential impact of changes of the above definition on substance vis-a-vis the texts in Ph.Eur has not been assessed.
- Potential impact of above definition for < *combined product* > on pre-MAA/development considerations:
  - Notified Bodies are not entitled to provide SA to developers.
  - The number of developments that cross multiple legislations is increasing, e.g. MP/device, MP/IVD etc. There is currently no tailored procedure for these products and compliance with more than one legislation is burdensome to applicants from a legal, procedural and scientific perspective. Medicinal product and device/drug evolve in parallel and are investigated in ONE protocol, yet, currently have to be submitted as separate trials according to the respective legislations. This results in independent timelines for the procedures, different documentation requirements and an artificial splitting of documents, that obscure the big picture of the respective development. The same issue arises where a medical device is actively investigated as comparator for a medicinal product in clinical trials, a situation seen in ATMP clinical trials (e.g. scaffold versus scaffold with cells)
  - Any proposal made at the level of MAA therefore must also be evaluated for its applicability during development as it should be in the interest of everyone to have these products developed in Europe rather than “just” approving/certifying products produced elsewhere. Any approach taken would have impact on the Clinical trials Regulation, the MDR and IVDR, however, could be justified from the perspective that the interface between these legislations has not or very insufficiently been addressed.
  - The ideal solution would be a single procedure for “dual legislation” developments, with consultation of respective experts organized by the National Competent Authorities in the background. Data arising from these trials should then be usable for authorization and certification purposes. This procedural solution would cause challenges in terms of submission to CTIS, as the data fields are currently not tailored for this purpose. The nature of the “interoperability” of CTIS and Eudamed required in the legislation has further currently not been defined.

## **2. Gene Therapy medicinal products**

*UNDER DISCUSSION*

## **3. Marketing Authorisations based on platforms**

### **3.1. Rationale for change**

- The current regulatory framework is designed to accommodate individualised medicines where the ‘individual element’ comes from (differences in) an autologous material used as starting material in the manufacture of this product; it becomes challenging where the adjustments are to be made based on characteristics of the patient or the causing pathogen. This partially also applies to

already certain authorised allergen products, for which disparity in the Member States' approach to authorisation of such large number of similar products under the current EU Pharmaceutical Law has been identified. Yet, it is expected that in the future some medicinal products may become even more 'individualised' therefore every effort should be made to ensure such products are not by default managed on a name patient basis or as magistral preparations without a due justification.

- There is a need to introduce the concept of "platform" MA and ensure single MAH oversight in the legal framework i.e. when a certain process /method is used to manufacture specific individualised treatments.
- There needs to be a distinction made between areas which may benefit from a 'master-file' type approach or a system allowing a degree of cross-referencing between dossiers and a specific platform-directed legislative approach with the difference between the different concepts defined.

### **3.2. Summary of proposals**

Under the concept of marketing authorisations based on platforms proposed in this CP, three scenarios are foreseen:

1. Platforms for the manufacture of some personalised medicines<sup>7</sup> ('one patient/group of patients-one product')
2. Platform for medicinal products against agents which are or have a potential to cause serious cross-border threats to health
3. Prior knowledge platform for medicinal products manufactured using prior knowledge, such as common manufacturing platform approaches.

Scenarios 1 and 2 intends to allow a difference in products under the same MA. Scenario 3 is not intended to accept differences in the same MA but to rely on some prior assessment by the authorities to avoid duplication of assessment, divergences and waste of resources. These concepts are independent and can be cumulative.

These new concepts whilst bringing additional flexibility should be seen as a derogation to the standard regimen. They should therefore be exceptional, interpreted strictly and be justified. Therefore, to qualify for the concepts above, the applicant will have to demonstrate the applicability of the platform concept with respect to the eligibility criteria proposed and justify that the related medicinal products warrant a single MA (scenarios 1 and 2) / support the transferability of the data in case of multiple MAs based on the platform (scenario 3).

For all concepts the 'platform' exists and therefore is authorised only within the scope of a MA and can only be submitted in conjunction with at least one MAA. Of note, scenario 3 is cumulative with scenarios 1 or 2 where relevant. The potential use of prior knowledge for these concepts does not provide a general waiver for product-specific data and it should be clear from guidance where these are required.

These 'platform' concepts should be defined in legislation to facilitate elaboration, in guidance, of the permissible specificities of the adaptations for related medicinal products for each concept. For all scenarios the platform comprises the standardised end to end manufacturing process of active substance and finished product which contains fixed and pre-defined intentionally variable components

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<sup>7</sup> Of note, this legislative proposal would only cover a subset of what may be considered personalised medicines described in a clinical context under [Health Research & Innovation](#), however this terminology was preferred over "tailored" or "individualised" medicines.

whereby the variable component can be part of the active substance and/or for the finished product. For personalised medicines, more details of the extended nature of changes which might apply, whilst still maintaining a platform concept are described below.

There are overlaps/impact of the scenarios developed here to other proposals in this and other concept papers. Notably concept paper 4 on novel manufacturing methods includes considerations on personalised medicines which link to this concept paper. Similarly, the use of master files described in concept paper 3, if agreed for excipients, active substances and raw materials, even if biological in origin, should be compatible with the platform concepts described below and the boundaries of both clearly aligned.

### 1. Platform for the manufacture of certain personalised medicines.

The current framework is based on the concept that a manufacturing process leads to a single product which is then provided to patients in a given indication(s).

Flexibility currently exists where a personalised element comes from e.g. autologous cellular starting material, leading to a patient-specific product based on a standardised manufacturing process.

Whilst some personalised medicines would be compatible with the standard MA regimen (e.g. autologous products, precision medicines<sup>8</sup>), there is a need for a dedicated framework to accommodate future personalised products within a single marketing authorisation in a given/related indication(s) encompassing personalised medicinal product(s) containing pre-defined active substance(s) for each patient/ group of patients. This would be based on personalised inputs, whether they are intrinsic or acquired (e.g. tumour-specific antigens in oncology, matching to HLA, DNA/RNA containing medicines) or where adaptation is required due to different pathogens in the respective patient. This new concept of platform would accommodate patient(s)-specific adaptations that would translate into adaptations in the medicinal product at the level of the active substance, starting materials, raw materials, manufacturing process, excipient(s), formulation, dose and strength and/or administration procedure. See concept paper 4 on novel manufacturing methods for specific examples of these.

For certain personalised medicines, different but related medicinal products could be part of the same marketing authorisation to treat patients in a single/related therapeutic indication only, when it is scientifically justified that the standard MA approach will not be adequate and it is demonstrated that the platform is maintained between products. This may result also in adopting special provisions in several areas e.g., PI, GMP/release of the finished product.

As highlighted above, this approach should be seen as a derogation to the standard MA approach only when the latter is not feasible. This should therefore be supported by clear eligibility criteria.

### 2. Platform for medicinal products against agents of biological origin which are or have a potential to cause serious cross-border threats to health

The recent pandemic experience has further exposed the need to rapidly respond to emerging health threats. Platform concepts for medicinal products against agents of biological origin which are serious cross-border threats to health can leverage platform experience to more rapidly facilitate authorisations in the context of large scale urgent medical need. This concept calls for extension of the provisions for coronavirus vaccines to more diseases.

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<sup>8</sup> Personalised medicines described here should be defined as distinct from medicines e.g. tumour-agnostic therapies, where off-the-shelf medicinal products (BRAF-inhibitors, immunotherapies, e.g. pembrolizumab, nivolumab) are selected for patient treatment based on selected biomarkers (e.g. high tumour mutational burden) detected via in-vitro diagnostic testing.



Similarly, for agents of biological origin which have potential to cause in the future, serious cross-border threats to health, use of a preparedness platform concept can ensure more rapid reaction in case of a potential public health emergency. This calls for extension of the influenza pandemic preparedness concept (so-called 'mock-up') to more diseases.

The development and authorisation of multiple versions of medicinal products (not only vaccines but other medicinal products also such as monoclonal antibodies) against a specific (biological) serious cross-border threat to health and its variants should therefore be facilitated within a single MA.

### 3. Platform for medicinal products manufactured using prior knowledge

For this scenario, the aim is to reduce regulatory burden for the resultant MAAs when relying on prior knowledge, accelerate assessment and foster consistency. Data derived from relevant experience in platform manufacturing (prior knowledge) for certain classes of molecules (e.g. transgene in a gene therapy vector, monoclonal antibodies (mAbs), oligonucleotides) for a given manufacturer should be leveraged to support development of other products based on the same manufacturing platform and expedite scientific assessment and approval.

Manufacturing platforms are promising enablers to translate scientific progress into medicinal products. Therefore, a legal basis for allowing and approving the use of prior knowledge (for quality, but also potentially non-clinical and clinical data), such as manufacturing platform approaches should be introduced. This is however only proposed for a platform based on the same standardised process including the complete end to end manufacturing process e.g. a mAb platform but not for an individual technology (e.g. an assay). This approach will have the benefit of stimulating development of products including for rare diseases.

Note: All three platform concepts could co-exist; for example, RNA-based neoantigen-specific therapy as individualised cancer immunotherapy manufactured for a specific patient (different transgene) could be captured under platform concepts 1 and 3.

### **3.3. Proposed solutions – in legislation**

As stated above, the proposal is to introduce 'platform' concepts within the legislation within the scope of a MA for a MP. It is not proposed to introduce a registration process for solely a platform technology, without an associated product. However, a legal basis to allow the use of prior knowledge (for quality and even non-clinical and clinical data, as relevant) is proposed. This approach will have the benefit of stimulating development of products for rare diseases or for infectious diseases even when they do not qualify for scenarios 1 and 2.

The three concepts are applicable to all types of MPs, whether chemical, biological or advanced therapy medicinal products.

From a quality point of view, the personalised or variable part of the standardised manufacturing process for the platform can be for part of the active substance and/or for the finished product. The extended nature of changes which might apply to personalised medicinal products are described below. A similar concept for the use of prior knowledge could be envisaged for (non)clinical considerations for all three scenarios, as relevant.

The proposed scenarios to be introduced in the legal framework are described below:

1. Platform facilitating the registration of eligible personalised medicines.

- This concept provides for a single marketing authorisation in a given/related indication(s) manufactured using a common platform technology but encompassing personalised medicinal product(s) for each patient/ group of patients.
- Adaptations for personalised medicines comprise a fixed and pre-defined variable component of the product tailored to intrinsic or acquired personalised inputs, from a patient or group of patients.
- These adaptations can be, but are not limited to, adaptations at the level of the active substance, starting material, raw materials, the manufacturing process, excipient(s), formulation, dose and strength and/or administration procedure (refer to concept paper on novel manufacturing methods for examples).
- When relevant, this concept should accommodate products resulting from decentralised manufacturing at multiple sites under a single quality system, (this is currently only described for ATMPs).

2. Platform for medicinal products against agents of biological origin which are or have a potential to cause serious cross-border threats to health.

- Serious cross-border health threats are as defined in DECISION No 1082/2013/EU in preparation for or during a pandemic event (or as expected to be defined in the proposed regulation on serious cross-border threats to health). This concept provides for two scenarios which could co-exist:
  - *Platform for medicinal products targeted to different existing disease variants/ strains: Expansion of the current provision for coronavirus vaccines.*  
The provision for coronavirus vaccines should be extended beyond vaccines and to other diseases i.e. by including medicinal products (e.g. vaccines and monoclonal antibodies) targeting several variants/related strains of an infectious agent within the same MA.
  - *Preparedness platform for medicinal products targeted to different variants/ strains that could arise in a health threat: Expansion of the current provision for influenza pandemic preparedness vaccines<sup>2</sup>.*  
The provision for pandemic preparedness vaccines should be introduced in the legislation within the spirit of Article 21 of REG (EC) No 1234/2008 whereby under such a platform "umbrella" MA, it would be appropriate to accept a MA or a variation to the terms of a MA, where certain non-clinical or clinical data are missing with a requirement for the MAH to provide the missing information upon marketing. This flexibility should be extended beyond influenza pandemic vaccines as proposed under the guidance section.
- Medicinal products using this platform concept are manufactured using a standardised process, have the same/ related indications and belong to the same MA from one MAH. A standardised process in this context refers to the complete end to end manufacturing process of active substance and finished product having intentionally pre-defined 'variable' components to accommodate the specific medicinal product with all steps remaining unchanged other than changes necessary to accommodate the medicinal product.

3. Platform for medicinal products manufactured using prior knowledge

- This concept provides for authorisation of platform-based medicinal products using prior knowledge to avoid duplicating scientific assessment by the authorities (i.e. using prior knowledge acquired).
- The registration of such platform would be linked to one MAH. The intent is to certify a manufacturing platform to avoid duplication of assessments in related MAs. This approach is therefore independent of the indications for the corresponding MAs.
- Medicinal products using this platform concept are manufactured using a standardised process, which refers to the complete end to end manufacturing process of active substance and finished product having intentionally pre-defined 'variable' components to accommodate the specific medicinal product with all other steps remaining unchanged other than changes necessary to accommodate the (medicinal product). It is not therefore applicable to an individual or group of technologies e.g. potency assays but should comprise the entire product platform.

Note: The introduction of this platform concept would facilitate authorisation of subsequent products from one MAH based on the platform knowledge (that could expand beyond quality data) and the core data package generated with approval of a first product, with additional quality, non-clinical and clinical data generated only related to the change to the product/novel indication. As the active substance is changed, this will be a new MA.

### **3.4. Proposed solutions – in guidance**

- There is no universally agreed definition of a 'platform,' therefore it is necessary to ensure that the final term used and the boundaries of the described concepts in the legislation are clearly defined.
- Process and guidance should be developed for MAHs and assessors to define how prior knowledge can be used for all platform concepts described.
- Under scenario 2, consideration should be given to providing an umbrella MA in this scenario which holds information on multiple strains by utilising the platform knowledge in Modules 3, 4 and 5 which would permit any of these strains to be marketed, when needed. This would also allow a degree of extrapolation for new strains, as needed, with a requirement that upon the MAH's request to activate the MA, further quality, non-clinical and clinical data are requested after marketing (as foreseen for influenza vaccines under Article 21 of Commission Regulation (EC) No 1234/2008).
- Guidance should clarify the eligibility, procedures and data requirements for products (product classes) which could use the respective concepts to support future MAAs. In particular, there is a need to illustrate which data are required to justify the concept and further, where flexibilities of data requirements and a risk-based approach can be applied. Depending on the specific approach taken, these flexibilities can be on the quality, non-clinical and clinical level. The concepts will only be used and successful if applicants perceive a lowering of the regulatory burden.
- For concept 2, eligible agents should be defined in guidance or in delegated acts. In addition, the possible extension to other high-risk scenarios (such as non-biological threats, potential seasonal vaccines (other than influenza) and anti-infectious agents could also be considered.

- For personalised therapies, guidance should make clear how ongoing data requirements for these therapies can be more contained after the bulk of the investment is made into the platform approach, making the platform commercially viable.
- Guidance should make clear that where prior knowledge is used across products for a platform, although these data need not be regenerated they may need to be re-submitted for each resultant product in the current framework to ensure sufficient lifecycle oversight pending availability of alternative submission tools such as cloud-based platforms.

### **3.5. Other considerations**

- Further reflection on definition of (new) AS in the context of personalised medicines is needed. However, it is proposed that products covered under the platform MAs scenario #1 and #2 as proposed above would fall under the same GMA regardless of whether they would be fitting the definition of a NAS (as for a new strain in the context of influenza); companies will however in exchange benefit from regulatory flexibilities that currently do not exist. then for platform #3 (prior knowledge), this would follow the usual rules linking to the determination of NAS.
- For any platform concepts introduced (which depending on the type of platform can link to multiple MAs or support different products within the same MA), there needs to be due consideration given to any post-approval changes for linked products in any future legislative framework that will facilitate streamlined life-cycle management changes for specific products/multiple products across the platform.
- The use of master files is compatible with the three concepts proposed, e.g. if the master file concept extends to starting materials of biological origin (e.g. vector backbone) or to a biological active substance or finished product, these could also be compatible with a platform approach. As stated earlier, boundaries between both concepts will need to be clearly defined.
- In the cases of platforms 1 and 2 where a certain level of variability may be allowed within the same MA, the active substance definition, changes in formulation, dosing and/or administration and implications for naming and labelling requires due consideration. Acceptable ranges e.g. for the active substance and finished product should be defined as part of the MA, resulting in a name (with qualifier) for the tailored medicine with separate product information (ePI). The nature of the PI may also depend on whether the product is tailored at an individual or group level.
- The above platform concepts exclude hospital exemptions.
- It is believed that some personalised products like certain bacteriophages could be accommodated into the personalised concept but may also fit within magistral preparations and/or as ATMPs if genetically modified and therefore careful consideration should be given as to the appropriate regulatory route for these products.

Note: The Commission could also consider the possibility to have a suitable framework for products developed for ultra-rare conditions that may never fulfil the requirements for registration including under the platform concepts listed above within the context of the Orphan legislative changes.

## **4. Active substance and excipients**

Current definitions: Directive 2001/83/EC Article 1

3a. *Active substance: Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.*

3b. *Excipient: Any constituent of a medicinal product other than the active substance and the packaging material.*

as defined in the EMEA/CHMP/QWP/396951/2006 guideline: „*Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances etc., as well as the constituents of the outer covering of the medicinal products, e.g. gelatine capsules.*”

#### **4.1. Rationale for change**

- Review definition of active substance and excipient to take into account technological progress and the possibility to introduce a subcategory (3c) of excipient, described as “functional<sup>9</sup>” excipient e.g. immune potentiation enhancers, permeability enhancers (hyaluronic acid, SNAC), and adjuvants should be considered.
- Products with “extended” concepts of active substance may not be appropriately addressed by the current definitions e.g. immune potentiation agents, permeability enhancers, MP targeting delivery systems, nanobots, etc. These are borderline devices/excipients, but which are functionally active and integral to the medicine (cover under AS/functional excipient/intermediate products).
  - Certain excipients with a functional effect e.g. adjuvants and lipid nanoparticles would benefit from being further reflected in Annex I of the Directive in order to define additional and specific data requirements that might apply. Currently the definition of excipient is broad and encompass all constituents other than the active substance and the packaging material. Hence there is a clear need to introduce a subcategory (3c) of “functional” excipient that would cover substances that have an activity that helps the administration and use of the medicinal product but does not contribute to the therapeutic activity on their own.
- There is also a need to clarify the conditions a substance otherwise pharmacologically active can be categorised as an excipient **or a subcategory of excipient, described in this paper as a functional excipient** – if not per se the active substance of the MP - when intended to exert an action complementing the activity of the AS and thereby indirectly contributing to the activity of the product (e.g. by increasing the absorption of the insulin, or adjuvants increasing the immunogenicity of vaccines) or with an action ancillary to that of the active substance/ingredient regarding the specified claimed indications for this medicinal product.

Note: The data requirements should be proportionate to the type of the substance used taking into account a risk-based approach (e.g. contamination risk for products from biological nature). The requirements for those substances that can be used in other medicinal products as an active substance should be clarified in technical guidelines including in terms of labelling, packaging. Of

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<sup>9</sup> The term “functional” excipient was not unanimous, but no suitable alternative could be agreed until now. Active excipient was deemed unsuitable due to the potential confusion with active ingredient, and critical excipient was also not supported by some MSs. There was a proposal for “highly functional” which was considered not preferred to functional and lately the term “key” excipient was also proposed but not discussed in details.

note, the FDA has also introduced the notion of “critical component” in relation to e.g. nanoparticles which they consider can have varied functions and contribute to the activity of the DP.

#### **4.2. Proposed solutions – in legislation**

- **Revision of Article 1 establishing conditions where the substance is considered an active substance, excipient, or as proposed below a subcategory of excipient (described for example as functional excipient or critical component that is not an active substance).** As part of this initial technical review, no change has been proposed to the definition of active substance.
- **Introduction under Article 1 (e.g. 3c) of a subcategory of excipient known as “functional excipient” that would not meet the definition of an active substance but contributes to, enhances the activity or performance of the medicinal product.**
  - The exact definition of a functional excipient will be of utmost importance and would be drawn to encompass for example vaccine adjuvants or permeation enhancers but not active substances that have a therapeutic contribution on their own (e.g. lidocaine when included in a medicinal product).
  - In connection with this proposal, the legislation should explicitly refer to the development of guidance, e.g. in the form of “In consultation with the Member States and the parties concerned, the Agency shall draw up and publish detailed guidance to address the criteria and requirements associated with these functional excipients”. Foreseen components falling within such category would include, but may not be limited to novel excipients, excipient of biological source and those described above that have an impact on the overall activity of the MP but not have a therapeutic contribution on their own, such as adjuvants and permeation enhancers. Further guidance and the impact of such subcategory of excipient on the overall activity of the MP would also need to be taken into account by developers of generic/biosimilar copies of MPs comprising such excipient when demonstrating bioequivalence between the two products that may not include the same excipients.
  - In connection with above-mentioned proposals any impact on increase of GMP requirements should be considered based on the potential underlying substance. With introduction of a functional excipient, similar requirements as established for API in terms of GMP requirements/inspection should be considered and to that effect, an explicit reference to enhanced GMP requirements with a cross-reference to the GMP guidance should also be included in the legislation.

Note: Please refer to the concept paper on master file to establish whether functional excipients would be eligible to master files.

#### **4.3. Proposed solutions – in guidance**

- Addition or revision of current definitions for novel excipients (including considerations for classification as novel), co-processed excipients, functional excipient, intermediate products, API mix, mixture of compounds, composites and associated requirements should be considered at guideline level.

Note: The proposal to address these aspects at guidance level rather than in the legislation is seen as an opportunity to make the legislation future-proof but also to allow for a wider consultation with all relevant stakeholders (for example supervisory authorities if needed).

- Potential need to develop new technical guidelines and revise Good Manufacturing Practice (GMP) guidelines and other quality guidelines depending on the changes implemented in legislation such as the creation of a subcategory of component (functional excipient) including:
  - Guideline on Summary of requirements for active substances in the quality part of the dossier,
  - Excipients in the dossier for application for marketing authorisation of a medicinal product,
  - Guidance on information to be provided for functional excipients in the Product information,
  - Guideline on manufacture of the finished dosage form etc.
  - Consideration for pharmacovigilance and safety signal detection for functional excipients (e.g. narcolepsy)

#### **4.4. Additional considerations**

- From a regulatory standpoint in the EU, active pharmaceutical ingredient (API), AS and drug substance are sharing the same definition according to the Notice to Applicant, volume IV, part I; however, the ICH Q6B definition of drug substance is not fully consistent with the EU / compendial definition of active substance and refer to product-related substances, product- and process-related impurities. It might therefore be beneficial to clarify the definition of API, AS and DS in Europe as well as therapeutic moiety.
- [Under inspections concept paper] Consider introducing ability to expand scope of inspection to functional excipients to facilitate regulatory oversight of such materials.
- [Under ASMF concept paper] Consider master file for certain excipient by analogy to ASMF, for novel and functional excipients particularly that are not already covered by a Ph Eur individual monograph.
- [Under product information concept paper] Ways to address functional excipients in the product information will need to be considered should the proposal be supported.

## **5. Biologicals (recognition of alternative manufacturing methods; synthetic)**

Current definition from Directive 2001/83/EC Annex I

*A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Indent 1 of Annex I to Regulation (EC) No 726/2004 Part A of the Annex to the regulation (EEC) No. 2039/93; advanced therapy medicinal products as defined in Part IV of this Annex.*

## 5.1. Rationale for change

- **Review the definition of a biological medicinal product considering technical and scientific progress.** Advances in analytical techniques as well as manufacturing technologies have been fundamentally improved and call for a re-evaluation of the strict relationship between process and product.
- **Clarify status of synthetic RNA/DNA based products and synthetic peptides and consider implications in terms of legal basis for their copies;** currently vaccines and other immunological products are considered to fall under biological MP. This argument cannot be used in case of synthetic RNA/DNA based products and synthetic peptides that are not an immunological or vaccine. For scientific and consistency reasons, it would appear logical if similar products were classified similarly to the reference medicinal products, independent from their source or whether they are immunologicals or not.

## 5.2. Proposed solutions – in legislation

- **Amend the definition of biological to move away from “the process is the product” and refocus on complexity** with the aim to link requirements with complex chemicals and include it in the definition section.
  - This new emphasis on the complexity of the product enables exemption of “simple” biological molecules from the requirements for biologics and render them subject to requirements applying equally to complex synthetic products. Implementing guidelines should therefore be drawn to clarify criteria to be considered for the assessment of whether a product would be considered complex or not, and those could be updated as science evolves. This approach would also not contradict the Ph.Eur. monograph “*Products of fermentation*” already exempting simple molecules from a biological source (indirect gene products such as amino acids, vitamins, antibiotics) from being classified as biologics. In pure regulatory terms, via such monograph, they are classified as chemical products. A list of those (non-complex) products of biological source would then be developed and maintained. See Section 5.3.
  - Secondly, the deletion of the product being defined by the process paves the way away from the paradigm ‘the process is the product’ and would be in line with the knowledge acquired for the last decades on biological medicinal products and the evolution of process understanding and analytical technologies. This will also help clarifying lifecycle aspects regarding production and different manufacturing sites, and the recognition of adapted or alternative processes for biologics that is essential for lifecycle activities and facilitate market access. The process will remain however, a crucial attribute of a biological product. Consequently, conditions where alternate manufacturing may be possible will need to be clarified in relevant guidance.

Proposed revision to the definition of biological MP (draft CP Dec-21):

*A biological medicinal product is a product, the active substance of which is a biological substance.*

*A biological substance is a substance that is produced by or extracted from a biological source **and due to its complexity** ~~that~~ needs for its characterisation and the determination of its quality, a combination of physico-chemical-biological testing, together with ~~the production process and its control~~ **strategy**. The following shall be considered as biological medicinal*



~~products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.~~

Proposed revision to the definition of biological MP (updated for final paper - Mar-22):

*A biological medicinal product is a product, the active substance of which is a biological substance.*

*A biological substance is a **complex** substance that is produced by or extracted from a biological source, **as defined in related detailed guidelines adopted by the Agency. Due to its complexity**, the characterisation and the determination of the quality or the biological substance may require a combination of physico-chemical-biological testing, together with the production process and its control **strategy**. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.*

- **Remove the description of per default biological products** e.g. vaccines, ATMPs in light of their potential to be synthetically sourced. However, should this change be implemented, Article 114 of Dir 2001/83/EC, which refers to the provision for batch testing for release by OMCL, may need to be adjusted to specify products that would be subject to batch release.
  - The concept of complexity would also be a basis to formulate requirements for vaccines or ATMPs from non-biological source.
- **Clarify the definition of immunological MP under Title 1, Article 1 (4)** and make it future proof by (option 1) updating or (option 2) removing examples to render it future proof.

Immunological medicinal product:

#### Option 1

Any medicinal product consisting of vaccines, diagnostic toxins, serums or allergen products:

(a) vaccines, diagnostic toxins and serums shall cover in particular:

- (i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;
- (ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;
- (iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergenizing agent.

#### Option 2

Any medicinal product consisting of vaccines, diagnostic toxins, serums or allergen products:

(a) vaccines, diagnostic toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as pneumococcal vaccines, Ebola vaccines, HPV vaccines, SARS-CoV-2 vaccines~~cholera vaccine, BCG, polio vaccines, smallpox vaccine;~~

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, tetanus anti-toxin~~anti-smallpox globulin, antilymphocytic globulin~~

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergen~~izing agent~~.

**Notes:**

- the addition of the term "diagnostic" to qualify toxins is intended to clarify the types of substances covered since not all toxins are immunologicals; e.g. Botulinum toxin as a neurotoxin does not fall into this category.

- a proposal is also to replace allergizing agent with allergen in the definition of an "allergen product".

### **5.3. Proposed solutions – in guidance**

- Guidance is needed regarding quality requirements for non-complex products of biological source, such as smaller peptides when manufactured based on fermentation using recombinant organisms. A list of products falling into this category would need to be developed and maintained by the Agency that could act as a reference for an exemption to the stricter requirements agreed for MPs meeting the definition of biologicals; the CMDh overview of biological active substances of non-recombinant origin<sup>10</sup> could be used as a starting point.
- The criteria and requirements for non-complex biologicals should be aligned towards those for complex chemicals and described in relevant guidance. There is an increasing number of products that could overlap between these two categories of products. (e.g. larger synthetic polypeptides, oligonucleotides, liposomal formulations etc). The current distinction between biologics and chemicals is therefore no longer sustainable in all cases. Guidance will need to be established for those two categories of products, complex chemicals and products from a biological source but not meeting the definition of 'complex' biologicals, considering possibilities for harmonisation.
- Guidance will need to acknowledge the above proposals and define specific requirements for complex "synthetic" medicinal products that would no longer fulfil the revised definition of biologicals, such as vaccines, but should continue to follow the requirements of biological products unless otherwise justified independently from the manufacturing technology.

### **5.4. Other considerations**

- The impact of the proposed classification as a (complex) biological or not as described above should also be considered in the revised post-marketing variation framework so that variations

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<sup>10</sup> [Microsoft Word - Compilation Biological Active Substance of non-recombinant... \(hma.eu\)](#)

for products issued from a biological source but excluded from the biological definition may not be automatically subject to stricter rules (e.g. classification as a Type II).

- FMT (faecal microbiota therapy) are currently variably classified in different member states, but widely used for e.g. treatment of C. diff infections often used by transfer with or without substantial modification from one or several human(s) to a recipient patient and with purposes corresponding to treatment or prevention of a condition. For preparation containing bacteria (or other microorganisms) as active principle the level of manipulation should be taken into account. There is also interest in engineered (could be recombinant / gene edited) bacteria for therapeutic use composed of viable microorganisms (bacteria, fungi, phages). Such products are variably classified by EU Member States so there should be a clear mechanism for member states to escalate to an EU classification panel in complex situations or when divergence occurs. In addition, EDQM could consider providing a quality and safety framework for microbiota.
- Pending resolution on the final definition of biologicals, ATMPs and vaccines, legal basis considerations for synthetic copies of such products will need to be addressed.

## 6. Industrial process

*Current text – Title II, Article 2 of Directive 2001/83/EC*

*1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.*

*2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.*

*Medicinal products derived from human blood or human plasma: Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.*

### 6.1. Rationale for change

- Advancing technology and innovative products challenge a single general definition of "industrial process" and raise the need for a more tailored approach.
- The introduction of "prepared on a non-routine basis" and hospital exemption as defined in Regulation (EC) No 1394/2007 has resulted in different interpretation in MSs; consider revising this derogation or develop additional guidance on the interpretation of the derogations/ hospital exemption clause.
- The current approach is also challenging also for bedside production, decentralized production.

### 6.2. Proposed solutions – in legislation

- Currently, the term industrial is used to limit the scope of the directive. However, as this notion was not further defined, different approaches were taken to interpret and to decide whether the directive was applicable. More clarity is needed, as well as sufficient openness to cope with future developments in the highly dynamic field of medicines.
- The drafting group initially considered the possibility to develop a definition of industrial process. In this reflection, the group took into consideration:

- the current interpretation (as per ECJ rulings)
- the need not to be restrictive vis-à-vis current and future developments in the highly dynamic field of medicines. For this, the emerging field of personalised medicines and bedside manufacture were taken as examples.
- **The proposal to the Commission is therefore to remove 'prepared industrially or manufactured by a method involving an industrial process' from the future legislation, and to focus on the derogations.** Indeed, further to the discussion and an attempt to come with a high-level definition (see below), the drafting group concluded to go rather for an '**all-in, except if specifically excluded (derogated)**' approach. As a result, small scale production for a few patients should be included, unless if clearly derogated.
  - On the derogations from the need for a marketing authorisation, the group considered that the current list in art. 3 is still appropriate, but a further class could be included as an additional derogation: *Tissue and cell preparation that are not substantially manipulated and are used in the same essential function in the recipient as in the donor.*
- **Hospital exemption clause: the DG regarded this as an important regulatory tool which should be maintained; it is felt however that the Commission should take the opportunity to revise this provision and ensure a more harmonised oversight between MSs.** It is also proposed that in addition of quality aspects, some proof of safety and efficacy (similar to what would be required for an early clinical trial) is required as part of the requirements for hospital exemption. These scientific requirements could be further expanded in guidance.
  - Apart from ATMPs under hospital exemption, other personalised medicines should not be included by default in the list of derogations unless meeting the existing definitions of magistral and officinal formula. It is also important to clarify that the proposed removal of a reference to industrial process has no bearing on those derogations.
- **The EC could include a definition of 'placing on the market'.** The group considered that for public health reasons, placing on the market should be interpreted broadly, i.e. any product given to the patients to treat, prevent or diagnose a disease. Placing on the market is therefore not to be restricted to medicines produced and marketed by a pharmaceutical company and any such products should be covered under the legislation. Further reflection is therefore needed on medicines produced by a hospital pharmacy for use in the hospital and medicinal products produced and used by the doctor himself for the treatment of his patients should be considered as placing on the market<sup>[1]</sup>In addition, this approach may ultimately drive the need for additional reflections on the remit of NCA supervision and GMP considerations vis-a-vis-hospital pharmacies.

Notes: Medicinal products prepared within a hospital are already in principle regulated by the present legislation, but the interpretation differs between countries and a clarification would be welcome. For example, many of these products are presently prepared within the derogations for magistral or official formulas for which however there is a clear disharmony between MSs in terms of oversight and pre-requisites ((See Section 8. ). This is something the Commission might consider addressing at EU level. Besides, the DG mentioned a few examples such as bacteriophages and allergen on site preparations that may not fit directly any of these definitions and for which there should be some harmonization on how they ought to be managed at national level.

<sup>[1]</sup> In Germany, the Länder consider this situation not as placing on the market.

### 6.3. Proposed solutions - in guidance

- It is proposed to include examples of products for which the pharmaceutical legislation applies and does not apply, by providing examples of products for which compliance with GMP is expected (e.g. radiopharmaceuticals).

### 6.4. Other considerations

- The below definition of industrial process is included for reference only as per the initial reflections within the drafting group, and is **not proposed to be included in the pharmaceutical legislation to define the scope:**

*Whatever may be the notion in the future revised pharma legislation, it should be ensured that the following approaches of manufacturing medicinal product are covered:*

- *medicinal products manufactured in significant quantities;*
- *medicinal products manufactured in smaller quantities and manufactured by means of complex or automated /medical equipment. This includes but is not limited to decentralised manufacturing and manufacturing at the bedside.*
- *personalised/tailored medicines produced using one or more standardised processes, though other steps may be non-standardised e.g. by changes necessary to accommodate the tailored medicinal product.*

Note: The EC may consider whether the above considerations may be useful in other contexts.

- The EC may consider a new harmonised framework to govern the “preparation/customisation” at the bedside/site of administration, which would include reconstitution and administration of MPs. This process is considered outside of manufacturing/GMP but could be very critical to the quality and safety/efficacy of the medicinal product. Such a framework and its scope could be briefly introduced in the legislation and technical requirements further elaborated in guidance (e.g. framework for assurance of correct administration, training material, instruction manual etc.). For this proposal, existing guidance such as the good practices for the preparation of medicinal products in healthcare establishments that is available for ATMPs (see Article 16.2 of Eudralex Vol 4. Guidelines on good manufacturing practice specific to ATMPs) could serve as a starting point. Scope may include ATMPs, personalised medicines, and the preparation of radiopharmaceuticals covered under Article 7 of [Dir 2001/83/EC](#).

## 7. Vaccine

Current references:

- European Pharmacopeia, Monograph of Vaccine for human use:

*Vaccines for human use are preparations containing antigens capable of inducing a specific and active immunity in man against an infecting agent or the toxin or antigen elaborated by it. Immune responses include the induction of the innate and the adaptive (cellular, humoral) parts of the immune system. Vaccines for human use shall have been shown to have acceptable immunogenic activity and safety in man with the intended vaccination schedule.*

- Directive 2001/83/EC article 1(4):

*Immunological medicinal product:*

*Any medicinal product consisting of vaccines, toxins, serums or allergen products:*

*(a) vaccines, toxins and serums shall cover in particular: (i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;*

- German Drug Law, section 4 (Definitions)<sup>[1]</sup>:

*Vaccines are medicinal products within the meaning of Section 2 sub-section 1, containing antigens or recombinant nucleic acids and intended for use in human beings or animals for the production of specific antitoxins and protective agents and, in so far as they contain recombinant nucleic acids, intended exclusively for the prevention or treatment of infectious diseases.*

## **7.1. Rationale for change**

- Absence of a clear definition for the term vaccine in the EU legislation has caused confusion in the past, especially as companies and other regulators may call vaccines also medicines intended to e.g., treat varying conditions from cancer to autoimmune diseases (like type I diabetes).

EMA has received queries from stakeholders and the public asking for clarification around the term vaccine that led to extensive internal discussions, with involvement of the Vaccines Working Party in 2012-2013 and then again in 2016. In these occasions, the VWP position was to limit the term vaccine to communicable diseases especially considering potential safety issues, e.g. linked to adjuvants, which could have a negative impact on vaccination strategies. However, there has never been an official position by EMA on this topic and this has led to the use of the term vaccine in other therapeutic areas e.g. in oncology guidelines for immunotherapy products. Regarding the latter, some concerns have been raised that, within the oncology field, the word vaccine could be used to promote false expectations of "prevention" of recurrences when this may not be proven. For all these reasons, at the time, the general consensus across working parties and the Agency was to restrict the term vaccine to prevention or treatment of infectious diseases.

- Currently, with new emerging technologies, there may be complex products which demand clear definitions in order to avoid confusion and repeated ad hoc consultations with subsequent waste of time and resources across expert groups. For example, there has been confusion about the classification of products which are intended to prevent or treat cancer caused by infectious agents such as HPV (e.g. a DNA vaccine intended to treat/prevent HPV cancer which was classified as ATMP without consultation with relevant experts), for which efficacy is measured in terms of both virological and disease progression endpoints (e.g., shrinking of the tumour) and which require specific expertise which goes beyond ATMPs. In addition, EMA has received queries from MSs who themselves receive questions from the public about e.g. the non-applicability of the term gene therapy to vaccines, illustrating well the lack of clarity around the term vaccine.
- There is also the need to clarify whether synthetic molecules may be considered as vaccines, which would impact handling of the assessment and definition of specific requirements for quality control. Details linked to this aspect could be clarified at the level of a guidance.
- It is generally agreed that the term vaccine should cover medicines that elicit an immune response against an infectious agent or toxin, i.e. that induce active immunisation against that agent/toxin, but this may not be a future-proof definition. Based solely on active immunisation as mechanism of

action, vaccines could belong to 3 categories:

1) for prevention, including post-exposure prophylaxis, of infectious diseases (the existing situation),

**2) for prevention, including post-exposure prophylaxis, and for treatment of diseases caused by an infectious agent,**

3) for prevention, including post-exposure prophylaxis, and for treatment of any diseases e.g. cancer.

Outcome:

- Concerning scenario 3, the following considerations were considered: extending the definition of vaccine to other non-infectious diseases would bring together products radically different in terms of benefit/risk considerations, clinical development and target population, scientific guidelines and requirements for authorisation. Moreover, classifying a medicinal product as a vaccine may have implications such as new requirements for official batch release, and expertise of the qualified person (QP). Even though the applicability of the latter two could be restricted in other ways, there would be no clear advantage to include immunotherapies under the umbrella of vaccines. For these reasons, scenario 3 is not considered a valid option.
- The drafting group and the vaccines working party considered that **scenario 2 reflects the most pragmatic definition based on current knowledge and experience with vaccines so far and in line with the research pipeline** e.g. vaccines intended for treatment of HIV- or HPV-infected patients but with no clinical signs of disease or which could target both prevention and treatment at the same time.

Note: Some experts flagged the case of the BCG “vaccine” used to treat bladder cancer.

Whilst this product has not been discussed in detail, these cases should be considered exceptions which may benefit from an *ad hoc* discussion and may not be referred per se as a vaccine per the current working definition. In addition, since it is not possible to forecast all future situations that may require additional clarifications, and in light of the rapid progress of medical science it was agreed that a definition in the legislation may not be easy to change rapidly, should there be the need. This was taken into account when making a final proposal to the EC.

- Regarding the term cancer vaccine, there was consensus that this should be avoided. The regulatory expectations for a product intended to protect against infectious disease is very different from those for a product intended to treat cancer by the induction of an anti-tumour immune response, including different efficacy and safety profile and public perception, and requirements for batch release. Therefore, even though the mechanism of action (inducing an immune response) is similar, widening the scope would only be sound from a classification point of view, but the two categories of products (against infectious disease and against cancer) would be assessed (endpoints), and handled very differently.
- Regarding the nature of vaccines, most vaccines are currently biological products, however it is possible that some constructs be made by synthetic process, e.g. some mRNA vaccines. **Both biological and synthetic antigens should be considered as vaccines.**

<sup>[1]</sup> [Drug Law \(pei.de\)](#)

<sup>[2]</sup> [Guidance for Industry, Clinical Considerations for Therapeutic Cancer Vaccines \(fda.gov\)](#)

## 7.2. Proposed solutions – in legislation

- **The current legislation should include a statement that the definition of the term vaccine is reflected in relevant scientific guidelines on vaccines issued by the Agency.** This proposal allows more flexibility so that it would be easier and faster to update the definition based on the need as research and technology evolve over time. Other options, i.e., to include a high-level definition, were discussed and rejected as they could create further confusion.
- Immunotherapy products inducing immune responses against diseases not caused by an infectious agent should not be considered vaccines. It is considered especially important that products inducing an immune response against cancer are not classified as vaccines and that the term 'cancer vaccine' is not used. A definition of immunotherapy product should be implemented in the legislation.
- With the proposed changes to the type of products falling under the definition of biologicals, **Article 114 of EC Dir 2001/83, which refers to the provision for batch testing for release by OMCL, may need to be adjusted** to this new proposal to specify products would be subject to batch release.
- Consideration to amend accordingly the definition of vaccines included in the European Pharmacopeia should be discussed considering the below agreed definition.
- **The gene therapy definition excludes vaccines against infectious disease.** This differentiation should be maintained due to the different mechanism of action by which vaccine exert protection against disease even when containing nucleic acids vs. gene therapies. In addition, the definition of ATMPs should be clarified in the legislation and exclude vaccines as per the agreed definition including e.g. cell-based therapies against infectious diseases, such as dendritic cells loaded with antigens.

## 7.3. Proposed solutions – in guidance

- Relevant guidelines should include the following proposed working definition of the term 'vaccine', together with the rationale as well as some examples; it should also clarify implications for cell therapies and batch release. For example, complex products with multimodal mode of action, e.g. products containing both a vaccine and a substance acting against both HPV antigens and cancer antigens respectively should not be considered as vaccines even though they partly meet the definition of a vaccine.

Proposed working definition:

*Vaccines are medicinal products which are **intended for prevention, post-exposure prophylaxis and/or treatment of disease caused by an infectious agent** and which contain antigen(s) or genetic information for an antigen(s), either of biological or synthetic nature, **that induce a specific immune response against the causative infectious agent(s) or its toxins.***

- Of note, the CHMP Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/) refers to cancer vaccines; all such guidelines should be aligned to the newly proposed definition:

*As such, in this extract of the above-mentioned guideline "E.g. **Immune therapies including therapeutic cancer vaccines** are aimed to induce specific anti-tumour immunity toward existing malignant disease. Such immune therapies are normally aimed to induce adaptive T and B cell as well as innate immune responses in cancer patients. The nature of the drug substances used is*



*highly variable, including synthetic peptides, recombinant proteins, virus-like particles, immune-modulating antibodies, gene therapy, and cell-based products. As it is difficult to break tolerance towards tumour antigens which are normally derived from self-antigens, cancer vaccines are often combined with pharmacologically active adjuvants such as cytokines or toll-like receptor agonists.”, the wording “vaccine” should not be used.*

#### **7.4. Other considerations**

- During scientific advice, developers should be referred to the relevant guideline and recommended to only refer to vaccine when aligned with the current EU working definition at the time of advice.
- Potential impact of early ‘classification’ as a vaccine for future extension of indications no longer fulfilling the definition may need to be addressed in relevant guidance.

## **8. Magistral formula and officinal formula**

### **8.1. Rationale for change**

- It was noted that disparities exist between Member States in the interpretation of these provisions (e.g. bacteriophages). Upon discussion by the drafting team, it was agreed that such problem would be solved if an adequate standard was agreed to and specifically for example if bacteriophage preparations were described in a pharmacopoeia although this may be considered challenging. It is noted also that some bacteriophage preparations might be compatible with the concept of platform MA and therefore might offer some opportunities for developers.
- There was also some discussion in the drafting team whether such preparations should explicitly be restricted to conventional pharmacy operations, but a clear majority was not in favour of introducing such restrictions to ensure the definition would remain future proof as what is considered complex and non-conventional now could in fact with the advance in technology become the norm in the future. However, with the caveat that depending on the nature of the operations, GMP considerations should be taken into account and homogenised across Member States.

### **8.2. Proposed solutions – in legislation**

- No change to the definition of magistral formulation was deemed necessary with the understanding that the term “pharmacy” capture both public/hospital and Community pharmacies; however, a slight clarification is proposed to be introduced for the definition of the officinal formula to differentiate from magistral formula and clarifies that the key criteria for an officinal formula lies with compliance with the pharmacopoeia, as follows:

#### Current:

*2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).*

#### Proposed:

*2. Any medicinal product which is prepared in a pharmacy in accordance with ~~a prescription and the~~ directions of the pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).*

Note: Under this definition, it is to be understood that such formula could be intended to an individual or group of patients and would cover both public and private pharmacies. In addition, it does not prevent Member States from imposing additional restrictions, such as the need for a medical prescription for also for officinal formulas a national level as this is currently not harmonized.

## **9. Allergen products covered under Article 5 of Directive 2001/83/EC**

Current text from Article 5 of Directive 2001/83/EC

*A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.*

### **9.1. Rationale for change**

- There is serious heterogeneity in the regulation of allergen products across Member States, especially with regard to preparations covered under Article 5 of Directive 2001/83/EC.
- There is widespread use of products for allergen immunotherapy not covered by a MA (as Named Patient Product (NPP) acc. to Art. 5 of Directive 2001/83/EC) without always sufficient proof of quality, safety, or efficacy. This is considered especially relevant as patients are treated with these products over several years.
- In most cases, no or few information on the number and type of NPP being on the market in MS is available.
- All products distributed in accordance with Article 5 without a marketing authorisation are currently fully excluded from the provisions of Directive 2001/83/EC.

Note: CMDh submitted proposals for changes to Directive 2001/83/EC to DG SANTE on 6<sup>th</sup> August 2021.

### **9.2. Proposed solutions in legislation**

- Clarification that allergen products shall be subject to a MA, as a personalised medicine and not be distributed according to Article 5 without marketing authorisation in a Member State in the case that alternative products for allergen immunotherapy to the same allergen source and for the same route of administration are available (in that member State). Member States may, only in exceptional circumstances and on public health grounds, grant exemptions from this provision. Considerations should be given to allow submissions of MAA at national level if the scope of the centralised procedure is extended to all NAS after a certain cut-off date.
- Article 5 should be revised such that the requirements as amended in Annex I (see following point) are applicable to allergen products that are distributed in accordance with Article 5 first point where this is specifically stated in the Annex I. The following statement could be added to Article 5: "For allergen products distributed in accordance with this article, regulations as set out in Annex I shall apply."
- Amendments should be made to Annex I Part III of Directive 2001/83/EC on

- General categories of allergen products for Allergen Immunotherapy (AIT) and in vivo diagnostics with gradual requirements for marketing authorisations.
- Requirement to submit basic information on named patient products being distributed to the national competent authorities.

### **9.3. Other considerations**

Please refer to the detailed proposal as submitted by CMDh to DG SANTE on August 6th 2021.

Note: it should be noted that a reference to the 10a legal basis would only be applicable in case that option 2 is chosen with regard to the restriction of biologicals to follow a 10a procedure as proposed in CP on generics and biosimilars (section 2.b.1).

## 10. Other considerations

- The legal status of Annex I of Directive 2001/83EC and its ability to be modified in a timely manner should be re-considered. Annex I already foresees a system of exceptions for dossier content for ATMPs and biologicals but may need to be further adapted to accommodate technological changes for complex combination products and systems, evolution of regulatory requirement including for variations (e.g. ICH Q12 and M4Q – summary below; go to CP 11 on functioning of the CP (Section 8) for details) and systems as well as future data submission /review modalities e.g. cloud based dynamic review. This could also facilitate re-use of data/cross-referencing foreseen under platform prior knowledge approaches and avoid duplications.
- An alternative might be to reduce the level of details in Annex I and address detailed requirements and potential for adaptations in separate guidelines, and/or Notice to Applicants.
  - The current definition of a 'variation' in REG (EC) No 1234/2008, Article 1 is "*any amendment to ... the information referred to... in Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto..* " however this may evolve in line with global development. In particular, to support the full implementation of the ICH Q12 Guideline on Lifecycle Management, the ability to differentiate between Established Conditions (information subject to variation if changed) and Supportive Information (not subject to variation if changed) within Module 3 dossier sections needs to be foreseen in EU legislation. As currently written, any change to module 3 content referred to in Annex I of 2001/83/EC triggers a variation.
    - (ref: [https://www.ema.europa.eu/en/documents/other/note-eu-implementation-ich-q12-guideline-technical-regulatory-considerations-pharmaceutical-product\\_en.pdf](https://www.ema.europa.eu/en/documents/other/note-eu-implementation-ich-q12-guideline-technical-regulatory-considerations-pharmaceutical-product_en.pdf) )
  - Dossier and data requirements are addressed at ICH and shall be referred to in guidance, such as the Notice to Applicant as relevant. For example, there is an ongoing revision of the ICH guideline M4Q (CTD on Quality) to version M4Q(R2). The concept paper was adopted in November 2021 and anticipated timeline for revision is 3-4 years. This will have a potentially major impact on the CTD structure for Modules 2 and 3,, which is currently defined in the EU legislation - Annex 1 of Directive 2001/83/EC and the relevant Eudralex vol 2B. Hence, a change to the level of detail or status of Annex I (as outlined above) will be necessary in order to enable implementation of ICH M4Q(R2).
- Need to broaden the source of clinical data that can be included in a MAA (regardless of the procedure type) by expanding the current perceived restriction under Dir 2001/83 Article 8 to "results of clinical trials" to other sources of evidence and also broaden the possibility to receive any type of data and information to make the legislation future-proof (See details in CP on functioning of the centralised procedure and RWE).

In addition, to optimise the quality of decision making, the Committees responsible for the evaluation of safety and efficacy of MPs should be entitled to request and review data from third sources upon their request in addition to the documents and particulars provided by the applicant

for data contextualisation and decision-making as long as the applicant is informed and has a right of access and comment to the data.

## 06. Concept paper for EC on **Inspections**

**Main theme:** Strengthening, simplification, adequate processes and support structures to make the best out of available resources – focus on requirements/processes sketched out in basic legislation.

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic lead	Experts from EMA
Drafting group	Experts from EMA, CHMP, GMDP IWG, GCP IWG, GLP IWG

## Recommendations for change

### **1. GMP and GCP inspection capacity and capability building (for human medicinal products)**

A shortfall in GMP and GCP inspection capacity in the EU network has been evident and these gaps have been further exacerbated because of Brexit and the Covid-19 pandemic (particularly for GMP inspections). In some cases, the lack of resources to conduct GMP inspections of EU interest (e.g. Covid-19 therapies, sites of risk and/or strategic importance, suspicion of GMP non-compliance) due to international travel restrictions and increased workload has caused significant delays to centralised regulatory procedures. As an outcome of Covid-19 pandemic, it is expected that EU GMP inspectorates will have to find strategies to manage a backlog of 3<sup>rd</sup> country inspections which can further impact the inspection capacity.

In addition to more inspection capacity, there is need for EU inspectors to develop expertise to inspect novel and emerging technologies: e.g. digitization, automation, artificial intelligence.

Solutions are necessary to promote and support extra inspection capacity and build inspector capability to strengthen GMP and GCP compliance oversight within the EU medicines network. *It is therefore proposed that changes to the legal framework are implemented to facilitate the creation of an EU pool of experienced inspectors in the Member States with the necessary expertise to conduct GMP and GCP inspections of EU interest in emergency situations, and when specific capacity and expertise is required. In this model the inspectors in the EU pool are part of the national competent authorities and delegated as a resource to the EU pool to conduct inspections in the scope (see below). This would require that the structure be supported financially by the EC to facilitate the participation of inspectors and to provide for on-going training of all inspectors in the EU network.*

Different models of how this structure can be organised have been discussed by the drafting group. For the purpose of this paper a decentralised model with inspectors located in Member States delegated to the pool of inspectors is proposed. It is noted that some Member States indicated during the drafting and IWG consultation exercise that they would not be supportive of a mandatory secondment scheme of national inspectors to an European taskforce. Therefore, should this initiative be pursued, further discussion with Member States would be required. *Furthermore, the IWGs emphasised the criticality of having financial support for the recruitment, qualification and training of inspectors to an implementation of such an approach and that commitment for this support towards this NCA is necessary before implementation.*

The Member States responsibilities (e.g. Supervisory Authority role for GMP) for verifying compliance with GMP and GCP within the framework of the centrally authorised products remain unchanged. The standard route for inspections to be conducted would remain through the current model and would account for the majority of inspection. The proposed EU pool of inspectors should represent an additional inspection resource available to complement the current inspection arrangements by conducting inspections to verify compliance with GMP and GCP standards and the MA dossier in emergency situations (e.g. public health crisis such a pandemic), if there is lack of capacity or capability (specific expertise). Inspections should preferably be conducted as a team of two Member States/NCAs and only exceptionally by one Member State/NCA alone. The EMA would be responsible to request and coordinate the inspections conducted by the EU pool.

In order for this EU pool of inspectors to be put together, Member States should be supported by an EU financial funding scheme so that, where possible, additional inspectors are hired. The funding should be ensured by the EU and contractually agreed. The required personnel resources should be defined and payment must be made in advance and independently of the actual demand.

The scope of inspections performed by the EU pool of inspectors are to verify ongoing compliance with GMP or GCP and the MA dossier for centrally authorised products for sites located in 3<sup>rd</sup> countries, or at the request of an EU Member State in the respective EU country in emergency situations, if there is lack of capacity and/or capability (specific expertise):

- (a) Pre-approval GMP inspections as part of a centralised marketing authorisation application or variation application especially those involving innovative manufacturing technologies is proposed for the first time.
- (b) For-cause GMP inspections where there are grounds for suspected non-compliance with EU GMP for centrally authorised products.
- (c) Routine or triggered GCP inspections, including any follow-ups, in 3<sup>rd</sup> countries for new MAAs, variations or in relation to Serious Breaches (SB)
- (d) Routine and triggered GCP inspection in 3<sup>rd</sup> countries, possibly joint with PhV inspections, for PASS/PAES (non-interventional studies)

If further relevant changes are made in the legal framework, additional tasks may include; pre-approval and surveillance inspections as part of an EU level emergency use authorisation procedure.

In addition to the proposals above, to facilitate inspections being carried out by the EU NCAs in 3<sup>rd</sup> countries when there are travel restrictions in place (i.e. during pandemic settings) support from the EC is needed to obtain special permission and access for inspectors at a diplomatic level to facilitate their travel (e.g. possibility to enter the country and no need for quarantine), receive local support in the country of destination (e.g. consulates) or special insurances as applicable. This support and approach is required to be applied to all inspectors conducting 3<sup>rd</sup> country inspections, not just inspectors part of the proposed EU pool.

### ***1.1. Proposed solutions – in legislation***

Introduce in Regulation 726/2004 and Directive 2001/83/EC (e.g. new legal provision to complement articles 8, 18, 19 of Regulation 726/2004 and Article 111 of Directive 2001/83/EC) the appropriate legal basis for a structure comprising an EU pool of experienced inspectors from the Member States to conduct inspections to verify compliance with GMP and GCP and the MA dossier for centrally authorised products, in case of emergency situations (e.g. public health crisis such a pandemic), if there is a lack of capacity or capability (specific expertise), under the coordination of EMA. The EU pool of inspectors should be supported by EU financial funding scheme to facilitate deploying additional inspectors in the Member States. The EU pool of inspectors and its organisational structure should be included in the Joint Audit Programme.

Funding for on-going training of all inspectors in the EU network (i.e. not limited to inspectors in the EU pool) to support the development of inspection capacity and expertise (e.g. implementation of novel technologies) is required.

### ***1.2. Proposed solutions – in guidance***

Appropriate guidance and procedures will need to be developed or amended to define the means of operation of the proposed structure, the interactions between the EMA and the National Competent Authorities as well as the scope/timeframe of the inspections that fall within the remit of the proposed structure.

For example, for GMP inspections the Compilation of Union Procedures procedure on the coordination of GMP inspections in 3<sup>rd</sup> countries would need to be amended to foresee the possibility for inspection requested by EMA to be conducted by the inspectors from the pool of inspectors by delegation from the Supervisory Authority.

## **2. Formal role for JAP for GMP and GDP inspections (mandatory participation of Member State, fixed periodicity financed by EC)**

The Heads of Medicines Agencies (HMA) agreed in October 2000 to set up of the Joint Audit Programme (JAP) as scheme to evaluate national inspection systems and ensure harmonised inspection standards and a harmonised approach to practical interpretation of GMP on the basis of European Union legislative requirements to support mutual recognition of inspection outcomes between Member States. Furthermore, the JAP has proven to be an essential tool for mutual recognition agreements (MRAs) and other international agreements as it gives evidence of a medicines regulatory system based on a network of Union agencies operating to best practice standards.



The JAP is however set-up as a voluntary scheme, with Member States requested to provide auditors and to support with conducting and reporting the audits while the auditee Member States bear the travel costs of the auditors. There is no obligation for auditees to accept the audits or to implement the corrective actions on the audit findings. NCAs provided the required resources (auditors) for conducting the audits. With increased workload with inspections and audits as well as the restrictions to travel during the pandemic, it has been even more difficult to identify NCA candidate volunteers to conduct audits.

Furthermore, as the JAP currently only covers GMP inspectorates, it would be a good opportunity to establish a Joint Audit Programme for Good Distribution Practices (GDP) Inspectorates as it is essential to build and maintain a robust legal pharmaceutical supply chain all over the EEA territory.

As such it is proposed that the audits under the JAP become a mandatory requirement, for both GMP and GDP, and be set out in legislation. GMP and GDP should be content of a combined JAP audit in the Member States.

It is therefore proposed that changes to the legal framework are also implemented to create a team of auditors (for GMP and GDP) from the Member state inspectorates that will be responsible to undertake the audits for JAP.

Furthermore, with a clear legal basis, the JAP programme and the pool of auditors should be fully and centrally funded by the EC to support Member States with developing additional resources for auditing. Furthermore, additional resources to conduct audits of MRA partners should be taken into account, as these audits are essential to ensure equivalent supervision systems.

Recognising that the Pharma Strategy covers only legislation on medicines for human use, it should be considered to also reflect, in the future, these proposed JAP revisions in veterinary legislation for harmonisation.

N.B. JAP is already referred to in the EU-US MRA

([https://trade.ec.europa.eu/doclib/docs/2017/february/tradoc\\_155398.pdf](https://trade.ec.europa.eu/doclib/docs/2017/february/tradoc_155398.pdf) ) and Israel ACAA (<https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:001:0002:0012:EN:PDF>) and the CETA with Canada also relies on this audit programme (<https://circabc.europa.eu/ui/group/09242a36-a438-40fd-a7af-fe32e36cbd0e/library/795cf9ad-898a-44dd-ad95-eb102f51f01b/details>).

Additionally, there is a cooperation agreement between PIC/S and EMA including harmonisation of the audit approaches and coordination of audit timing (no duplication)

([https://www.ema.europa.eu/en/documents/other/co-operation-between-pharmaceutical-inspection-co-operation-scheme-european-medicines-agency\\_en.pdf](https://www.ema.europa.eu/en/documents/other/co-operation-between-pharmaceutical-inspection-co-operation-scheme-european-medicines-agency_en.pdf) ). There is a letter of agreement signed by PIC/S and HMA, which entered into force on 15 August 2016, by which HMA and PIC/S agree to cooperate in exchanging information in the context of the EEA Joint Audit Programme (JAP) of GMP Inspectorates and the PIC/S Joint Reassessment Programme (JRP) of Participating Authorities.

## ***2.1. Proposed solutions – in legislation***

Proposed change to Directive 2001/83/EC to introduce a requirement that competent authorities are subject to regular audits conducted by other Member States (the EU/EEA audit team) to maintain an equivalent and harmonized implementation of the EU legislation concerning GMP and GDP and corresponding enforcement activities. Audits should be followed up until satisfactory completion of all corrective and preventive actions identified during the audit and required to ensure an appropriate implementation of relevant provisions of European Directives into national laws and equivalence with other EEA GMP inspectorates. The JAP programme should be fully and centrally funded by the European Commission.

Considering the fact that the audits and the implementation of the CAPAs become mandatory, support for the auditee Member State at the end of the audit to implement the CAPAs should be proposed whenever necessary and funded by the Commission.

Acceding new Member States should also be subject to such audits and a positive outcome should be a condition for accession to the EU and in order to verify legislative and regulatory alignment to EU systems.

*Changes to Directive 2001/83/EC should be implemented to require that:*

- *a team of auditors is put together and appropriately trained by delegation from the Member state inspectorates to undertake the GMP and GDP audits for JAP.*
- *The Member States are audited on a regular basis (to be defined)*
- *The implementation of the CAPA resulting from the audit is mandatory*
- *Support for CAPA implementation can be requested*
- *The programme and CAPA implementation by NCA are funded by the European Commission*
- The secretariat and coordination is ensured by the EMA.

## **2.2. Proposed solutions – in guidance**

Guidelines and procedures for the operations of the JAP under the umbrella of the Compliance Group of the GMDP IWG are already in place. Existing guidance would need to be updated to reflect the change in legislation, and adapted where necessary to foresee the introduction of the JAP for GDP.

The update should support having qualified auditors to perform the audits. The guidance should support the following areas:

- How to get qualified auditors
- How to encourage Member States to provide human resources to participate in the whole process (qualification of auditors, participation in audits)

Member States should receive financial compensation for the activities in supporting the JAP programme, in addition to the payment of transport, accommodation and meals by the auditee. An EU wide system of fees similar to that used for assessment of centralized MA products could be considered.

## **3. Legal basis for reliance on trusted non-EU regulatory authorities GMP inspection outcomes and for other control measures other than on-site inspections**

The use of outcomes of GMP inspections carried out by trusted non-EU regulatory authorities as a means of verifying GMP compliance by EU authorities has increased during the pandemic when travel restrictions were in place. The use of alternative inspection practices such as inspection reliance<sup>1</sup> on

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<sup>1</sup> Reliance is understood as the process through which an EU Supervisory Authority can use inspection outcomes from trusted non-EU regulatory authorities, whose standards of GMP are equivalent to those in the EU (outside the established framework of Mutual Recognition Agreements or equivalent) as part of their risk based inspection programme.

other inspection outcomes for other authorities, desktop reviews<sup>2</sup>, distant assessments<sup>3</sup> and hybrid inspections<sup>4</sup> have increased in the last couple of years. As a lesson learned from the pandemic, these alternative inspection practices should continue to be used on risk based approach to avoid duplicative inspection efforts while maintaining the supervision of manufacturing sites, and allow a more efficient use of inspection resources.

The current legislation (Art. 111 of Directive 2001/83/EC) requires that:

- manufacturers located in the EU and in 3<sup>rd</sup> countries are subject to repeated inspections based on risk, and
- manufacturers or distributors of active substances located in third countries , whenever there are grounds for suspecting non-compliance.

The legislation (Art. 111 (5) and (7)) foresees that after an inspection a GMP certificate or GMP Statement of Non-Compliance is issued.

The legislation does not define at what frequency such inspections need to take place but specifies that such inspections are based on risk. While Directive 2001/83/EC does not specifically require EU GMP certificate for a regulatory submissions, in practice GMP certificates are used as standard for regulatory submissions (e.g. marketing authorisation applications, variations). However, it is recognised that GMP compliance of manufacturing sites in third countries may also be confirmed through other means, such as based on information on GMP compliance from trusted non-EU regulatory authorities (e.g. MRA partners, PIC/S Members).

Some Member States have implementing national legislation which is more restrictive than the requirements set out in the Directive 2001/83/EC. Therefore, there is a lack of harmonised approach between Member States which can lead to different outcomes (e.g. especially for the centralised procedure). The national legislative requirements for these Member States would need to be updated and harmonised before the concept of reliance can be fully implemented.

The legislation on GMP inspection is complemented and further detailed in the procedural guidance included in the Compilation of Union Procedures (CoUP).

A parallel is drawn to Article 8 of Directive 2002/98/EC and the approaches taken concerning inspections of blood establishments on human blood and blood components. The Directive makes reference to “inspections and control measures” conducted regularly of establishments to ensure compliance.

Considering the above, it is proposed to include a reference in the EU legislation on the possibility for EU authorities to rely, as part of their risk based inspection programme, on inspection reports from trusted non-EU regulatory authorities (whose GMP compliance programmes<sup>5</sup> are equivalent to those in the EU). Both compliant and non-compliant inspection outcomes from such non-EU regulatory authorities should be taken into account. The EU Authorities would use reliance on a case by case basis (e.g. as part of a desktop review exercise) when required, and not as an automatic reliance on all outcomes by the trusted non-EU regulatory authorities.

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<sup>2</sup> A desktop review is an exercise through which GMP compliance of a site is confirmed through review of relevant documents ( including inspection reports from third country authorities), without the inspectors being physically present on site.

<sup>3</sup> A distant assessment is the verification of the compliance of a site on the basis of interviews and documents, supported by technology for communicating, accessing systems, sharing and reviewing documents and other information, without the inspectors being physically present at the sites, as per EMA/335293/2020 –Guidance related to GMP/GDP and PMF distant assessment.

<sup>4</sup> A hybrid inspection is a mixed process were an on-site inspection is conducted alongside distant assessments.

<sup>5</sup> term used for JAP and JRP (Joint Re-assessment procedure by PIC/S) assessments and encompasses : legislation, regulatory policy, GMP standards, inspectorate resources, training, inspection procedures, enforcement, surveillance, analytical capability and QMS.

The trusted non-EU regulatory authorities should be designated based on specific criteria confirming equivalency of the GMP compliance programme framework (e.g. PIC/S Members or strategic partners(MRA)) and included by the Commission on a list, similar to the approach taken for the API white listing.

In addition, to support the implementation of alternative inspection approaches, a reference on the possibility for sites to be supervised by inspections and other justified control measures should also be included in the legislation. Given the implications on regulatory submissions, it is recognised that changing the approach for confirming GMP compliance for sites (i.e. change to inspection frequency, reliance on trusted non-EU regulatory authorities, desktop reviews) needs to be communicated to assessors who require this information to approve regulatory submission. Therefore, it is acknowledged that it is critical to establish communication channels and tools to ensure this information is appropriately exchanged between inspectors and assessors.

As such, the proposed revisions to legislation would need to be further complemented by appropriate guidance.

### ***3.1. Proposed solutions – in legislation***

The following changes to Directive 2001/83/EC can be considered for implementation of the concepts in legislation:

1. Revision of article 20 to include a provision that the competent authorities may rely on inspection reports from trusted non-EU regulatory authorities as part of their risk based inspection programme according to the detailed guidelines laying down the principles applicable to inspections referred to in Article 111a. To support a consistent and harmonized approach to reliance between the different Member States, the non-EU regulatory authorities who are considered to be equivalent should be selected by the Commission based on specific criteria and included in a list.
2. Revision of article 111 to include a provision that manufacturing sites can be supervised by means of repeated inspections and through other control measures (wording can be adapted). Such wording would provide the legal reference to allow for further definition in guidance for other means of verifying GMP compliance such as reliance, desktop review, distant assessments and hybrid inspections.

Since there are EU Member States whose national legislation is more restrictive, such changes would require, as appropriate, the update of national legislation to provide the legal basis for NCAs to rely on inspection outcomes from trusted non-EU regulatory authorities and to supervise manufacturing sites by means other than inspections.

### ***3.2. Proposed solutions – in guidance***

Updates to the inspections procedures in the Compilation of Union Procedures will be necessary to define inspection reliance and the other control measures and how these can be applied as means of verifying GMP compliance.

The procedures in CoUP can clarify under which conditions these approaches can be used (e.g. for which types of sites and operations, and how long on-site inspections can be deferred). Such harmonised procedures are necessary to support the recognition by other EU Member States of the outcome of the exercise conducted by another Member States.

Moreover, a harmonised way of recording the outcome of reliance on a 3<sup>rd</sup> country authority will be necessary (i.e. recording an entry in a database, such as EudraGMDP) to allow Member States to check and rely on the exercise conducted by another EU authority.

Lastly, assessors will require clear instructions as to when a site can be considered GMP compliant when reviewing regulatory submission. An important change to the current approach to GMP certificates and their validity is to ensure the outcome of such inspection measures will be appropriately communicated to assessors.

## **4. GCP inspections – provide clear criteria for when GCP inspections are required prior to MA approval**

There is no need to change legislation because there is guidance available to indicate the criteria for when routine and for cause GCP inspections are required prior to granting of a marketing authorisation: “Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for “routine” and/or “for cause” inspections, their investigation and scope of such inspections” (EMA/INS/GCP/167386/2012)”. This document will be kept updated as new criteria elements are identified.

### ***4.1. Proposed solutions – in legislation***

This is not applicable.

### ***4.2. Proposed solutions – in guidance***

This is not applicable.

## **5. Considering the use of tools and techniques for Bioequivalence inspections**

Identifying data manipulation through a bioequivalence (BE) inspection is very difficult which poses a challenge to inspectors. A systematic use of supporting IT tools to help identify data anomalies in pharmacokinetic trials would help address this issue.

### ***5.1. Proposed solutions – in legislation***

This is not applicable.

Please refer also to point 6 on GCP.

### ***5.2. Proposed solutions – in guidance***

EMA guidance and procedure documents on bioequivalence inspections could be updated to reflect the possibility of systematic regulatory use of IT tools for fraud detection in bioequivalence (BE) trial data, with the possibility to be supported by the acquisition at EMA and/or NCAs of the analytical software used for chromatograms reading and the assessment of BE trial data.

## **6. Ensuring MAH responsibilities are explicit in respect to contracted services (GCP (including BE), GLP, PhV and GMP)**

### **GCP, GLP and PhV**

The current challenges are around the remit of EU inspectors to review documents, access files and systems located at service providers (incl. IT vendors of computerised systems) involved in the development, manufacturing and post-market surveillance of the medicinal products (or life cycle)..

#### ***6.1. Proposed solutions – in legislation***

In order to address the challenges for EU regulatory authorities to obtain information directly from service providers (e.g. clinical research organisations (CROs)), Directive 2001/83/EC should be updated to include the requirement for the Applicant/Marketing authorisation holder (MAH) to have contracts in place with such service providers, requiring the Applicant/MAH to audit the service providers and ensuring that regulatory authorities can inspect, whenever required, (part of the) sites or electronic systems of the service providers that perform tasks on behalf of the applicant/MAHs. In addition, it should be explored if the Directives and Regulation could also be updated to reflect the possibility for regulatory authorities, in the context of a regulatory procedure, to request documents and ask questions directly to service providers without affecting the responsibilities of the Applicant/MAH.

#### ***6.2. Proposed solutions – in guidance***

The details of the requirements for contractual arrangements are to be defined in guidance documents.

### **GMP**

The recommendations of the lessons learnt from the presence of N-nitrosamines in sartan medicines included proposals for several revisions or clarifications of guidelines as well as possible changes to legislation during implementation, including initiatives to ensure that MAHs and manufacturers fulfil their legal responsibilities with respect to the quality of their products.

Some of these responsibilities were clarified in the “Reflection Paper on Good Manufacturing Practice (GMP) and Marketing Authorisation Holders (MAHs)”, which was finalised and published in July 2021 (Ref. EMA Document No. EMA/419517/2021). That paper focuses on the GMP-related responsibilities that apply to MAHs; while it recognises that MAHs are usually not directly engaged in the manufacture of medicinal products. It addresses the fact that MAHs have a large number of GMP responsibilities nonetheless, including a clear role in facilitating GMP compliance.

Article 111 of Directive 2001/83/EC requires the competent authorities, in cooperation with EMA, to ensure that the legal requirements governing medicinal products are complied with, through means of inspections and other activities. This article is relevant to MAHs, as its paragraph 1d explicitly empowers Member State authorities to inspect MAH companies.

However, while Article 111.1d provides the legal basis for such inspections, there are currently no further details in the legislation about such inspections, and neither is there any procedure in place at EU level setting out the norms for such inspections. This has led to the situation whereby there is no harmonised approach across the Member States to inspecting MAHs in relation to their GMP responsibilities; some Member States currently inspect MAHs, whilst others appear not to. MAHs are a major stakeholder group with significant pharmaceutical regulatory responsibilities, but, outside of

pharmacovigilance and clinical trials, it is evident that those companies are subject to very varying degrees of regulatory oversight. Given the extensive role that MAHs have in placing batches of medicines onto the market, and given their general responsibilities for the safety, quality and efficacy of medicinal products, as clearly spelled out in Annex 16 to the EU GMP Guide, this is not a satisfactory situation.

### **6.3. Proposed solutions – in legislation**

Proposed changes to Article 111.1d should be considered to further detail the circumstances and scope of inspections of MAHs; this could be similar to the language used in Article 123 of the new Veterinary regulation, 2019/6, which addresses this area in more detail.

### **6.4. Proposed solutions – in guidance**

In addition to the proposed revision to the legislation, it is proposed that detailed guidance on conducting inspections at MAH premises by the Member States is developed in the CoUP, to achieve a harmonised approach between NCAs.

While the Reflection Paper on GMP for MAHs is a useful source of information for MAHs about their responsibilities (and while it is also useful for competent authorities performing MAH inspections), its location in Part III of Eudralex Volume 4 means that it does not have the status of being official guidance that is expected to be followed by MAHs. This may limit its effectiveness. It is proposed, therefore, that the reflection paper be transformed into a new Annex to the EU GMP Guide, and moved into the Annexes section of Volume 4.

## **7. GMP Inspections of critical starting material and excipients**

The legal framework allows for GMP inspection of finished product and active pharmaceutical ingredient manufacturers. However, the current legal framework does not make provision for inspection of some critical starting materials (e.g. viral vector) used in the manufacture of genetically modified cells where the cells are critical to the quality of an advanced therapy medicinal product. The lack of a firm legal basis to inspect manufacturers of critical starting material (such as viral vectors) and to determine the level of GMP compliance at such manufacturers under the current legal framework, is of major concern to EU competent authorities.

A Question and Answer guidance on 'Principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs', addressing these concerns, was published on the EMA website for stakeholders.

However, the Member States formally requested the EC to change the legal framework at the next revision of the pharmaceutical legislation in order to make provision for inspection of sites responsible for manufacturing of critical starting materials<sup>6</sup>. (letters to the EC sent 12<sup>th</sup> June 2020 and 5<sup>th</sup> October 2020).

In addition, the current legal framework (Art.111 (1)(b)) allows for GMP inspections of active pharmaceutical ingredients and excipient manufacturers when there are grounds for suspecting non-

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<sup>6</sup> Blood/plasma and tissues / cells as starting material are covered by Directive 2002/98/EC and 2004/23/EC and are not concerned by this concept paper.

compliance with the legal requirements laid down in this Directive, including the principles and guidelines of good manufacturing practice and good distribution practices referred to in point (f) of Article 46 and in Article 47.

This does not make provision for inspections of manufacturers of some critical excipients (e.g. excipients lipids for m-RNA) which might be deemed necessary in the context of the assessment of a new product application.

Manufacturing sites for starting materials or excipients are not required to hold a manufacturer's authorisation. However, should an inspection be carried out for critical starting material or excipient a GMP certificate could be issued by the NCA.

### **7.1. Proposed solutions – in legislation**

Strengthen provisions of Article 111 of Directive 2001/83 for inspection of manufacturers of critical starting materials, such as viral vectors and excipients.

The proposed change for the legislation would be to strengthen the provision article 111 1b, to indicate that inspections of critical starting materials and excipients can be conducted when it is considered necessary. Please see an example below:

**Whenever it is considered necessary** and when there are grounds for suspecting non-compliance with the legal requirements laid down in this Directive, including the principles and guidelines of good manufacturing practice and good distribution practices referred to in point (f) of Article 46 and in Article 47, the competent authority may carry out inspections at the premises of:

- (a) manufacturers or distributors of active substances located in third countries;
- (b) manufacturers or importers of excipients.

**(c) manufacturers or importers of critical starting materials**

### **7.2. Proposed solutions – in guidance**

Amend the compilation of Union Procedures to include guidance when it may be considered necessary to inspect critical starting materials and excipients.

A definition based on risk of critical starting material should be established in the guidance in order to define when an inspection can be performed by Competent Authorities. Additionally, a change of section on starting materials in relation to plasmids and viral vectors in the GMP guideline for ATMPs would be necessary.

## **8. Triggers and criteria for GLP pre-approval inspections in the centralised procedure**

The non-clinical safety studies used for regulatory decisions should be GLP compliant in the current European regulation.

EMA GLP IWG in relation with SWP and CHMP issued, in March 2015, a checklist designed to be used by assessors when reviewing non-clinical safety studies and environmental risk assessment studies in order to detect the need for GLP study audits (EMA/89741/2015: Triggers for audits of good laboratory practice (GLP) studies). Moreover, OECD GLP WP issued in July 2019 another document dedicated to



Receiving Authorities with the same purpose (ENV/JM/MONO(2019)25: Guidance Document for Receiving Authorities on the Review of the GLP Status of Non-Clinical Safety Studies).

Despite of such guidance, it is noted that very few GLP triggered inspections had been requested by CHMP during the centralised procedures of MAA assessment. This fact could be explained by two reasons.

Firstly, at the MAA procedure stage, some of the non-clinical safety data are superseded by clinical data and triggered inspections on non-clinical safety data have in that case no added value. Nevertheless, some toxicological endpoints (genotoxicity, reprotoxicity, carcinogenicity, etc) are not covered by clinical trials. The efforts in assessment of non-clinical safety studies may be encouraged at the clinical trial authorisation stage. For example, the content of the dossier for such authorisation could explicitly request that at least the lists of the non-clinical safety studies in support of the authorisation submission and the location where and when they have been conducted (dates, name of the test facility and country), as proposed in Q&A No. 1.17, draft FAQ document version 4.1 on Clinical Trials Regulation (EU) No. 536/2014, and not only a general GLP compliance statement from the Applicant. Such proposal concerns the Regulation (EU) n° 536/2014 on clinical trials on medicinal products for human use, and not Directive 2001/83/EC which does not need to be modified.

Secondly, it is easy for the non-clinical assessors to detect the studies not declared as GLP compliant or that have been conducted in a test facility located in a country not adherent to the OECD Mutual Acceptance of Data agreement (a mutual acceptance managed by OECD in which GLP compliant studies conducted in one Member country should be accepted as GLP compliant in another Member country). It is more difficult to detect from the final study report in pdf format only the reliability and integrity of the data, the test system variability, or the study data too clean or too messy, the implausibility of data provided, the overall intra-test system variability or results that contradict published or known data.

Moreover, centralising GLP triggered study audits at EMA level would save resources by avoiding each country to conduct them, especially when the studies are submitted for clinical trials applications.

### ***8.1. Proposed solutions – in legislation***

To help the non-clinical assessors, even the GLP inspectors, to review the non-clinical data, it could be suggested to add a requirement in Annex I of Directive 2001/83/EC, in chapter about Module IV, that upon request of the assessors, non-clinical safety data should be provided by the Applicants in an electronic format that allows assessors to make calculations to detect inconsistent, atypical or too smooth data, and not only the final reports in pdf format as requested in the current regulation. The next step behind this idea is to provide assessors and inspectors with tools to analyse the data and with libraries of historical control group data of each strain of animals or other biological test systems used in GLP non-clinical safety studies. To compare with the rest of the world, US FDA already requests non-clinical safety data to be submitted in a specific format (SEND) that allow such analysis and triggered request for GLP study inspection by US FDA are done on a regular base.

### ***8.2. Proposed solutions – in guidance***

A template could be issued by EMA in collaboration with the GLP IWG and the SWP to request the triggered study audit, with a focus on what information is requested by the assessor.

The implementation of IT tools at EMA level to automatically analyse the submitted non-clinical data and compare them to data bases of historical data could facilitate the detection of strange data. These IT tools could be useful for non-clinical assessors and GLP inspectors.

## **9. Strengthening the Legal Basis for the Sampling of Active Substances and Medicinal Products and Provision of Essential Materials**

One of the recommendations made in the EMA/HMA Sartans Lessons Learnt report (full title: 'Lessons learnt from presence of N-Nitrosamine impurities in sartan medicines') dated 23 June 2020 is related to strengthening the legal basis for active substance sampling. The exact recommendation (No. 16) is as follows:

*Ensure the retention and availability of samples of active substances and excipients used during the manufacture of a given medicinal product batch and consider the possibility of strengthening the legal basis for active substance sampling.*

It is noted that Article 111.1g(b) of Directive 2001/83/EC provides a legal basis for the taking of active substance samples during inspections. It refers to inspections carried out by officials representing the competent authority at manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the holder of the manufacturing authorisation. This article empowers the competent authority to take different kind of samples during such inspections, including with a view to independent tests being carried out by an Official Medicines Control Laboratory (OMCL) or a laboratory designated for that purpose by a Member State.

This article is limited in that it links the taking of samples of active substances or other samples with inspections – there is no provision for sampling outside of an inspection at manufacturing sites. Practical experience when organising national or OMCL Network-wide market surveillance testing activities and in recent years also when dealing with the nitrosamine cases have shown that there are occasions when there is a need to request in particular active substance samples very often in conjunction with corresponding drug product samples to be tested in OMCLs outside an inspection. It would therefore be needed to have a clear legal basis for taking samples independently from an inspection. It would also help if there was a clear provision to empower OMCL staff to perform the requesting of samples – not just competent authority staff.

Additionally, experience has shown that it is sometimes difficult to obtain other essential materials (e.g. reference standards or specific reagents) that are required for testing. It would be useful if there was a clear legal basis for the competent authority, EMA or an OMCL to make requests for such materials free of charge from the marketing authorisation holder.

It is noted that Article 19.2 of Directive 2001/83/EC empowers the competent authority during the pre-authorisation phase to submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose. This is in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with Article 8(3)(h) are satisfactory.

While this is useful, there is no clear legal provision that requires the applicant to comply with requests from the competent authority, EMA or OMCL for materials such as reference standards or reagents, essential for carrying out testing. This legal obligation should also apply to post-marketing testing activities as foreseen in Article 111.1g(b).

### **9.1. Proposed solutions – in legislation**

The following changes are therefore proposed to be considered to address the above points:

Article 111 of Directive 2001/83/EC: to make a change to include the possibility for samples to be requested outside an inspection upon request by a competent authority, EMA or OMCL (in agreement with the corresponding NCA, as applicable) including any required essential material; furthermore, to require Marketing Authorisation Holders/manufacturers to comply with such requests.

Article 19.2 of Directive 2001/83/EC: to add a provision stating that the applicant should comply with requests from the competent authority, EMA or OMCL (in agreement with the corresponding NCA, as applicable) for samples and accompanying essential materials.

### **9.2. Proposed solutions – in guidance**

In addition to the proposed revision to the legislation, it is proposed that detailed guidance on the sampling of active substances and medicinal products and the provision of essential materials be developed to achieve a harmonised approach between competent authorities and the OMCLs.

## **Additional Recommendations for legal changes not related to Directive 2001/83/EC and Regulation 726/2004 for future consideration**

### **10. Legal remit of EU inspectors to access trial participants documentation at sites located outside the EEA, if the informed consent signed by the trial participants does not explicitly mention EU regulatory authorities' access to their personal information and medical records**

Current challenges:

The Commission Implementing Regulation (EU) 2017/556 established detailed arrangements for inspection procedures with regard to GCP, including powers of the inspectors responsible for the review. Article 7 states that the inspectors should be granted the necessary powers of access to the premises and data (and contact trial subjects in justified cases).

For inspections in 3rd countries these powers remain uncertain, unless the signed informed consent form established such authority. This has resulted in uncertainty, delays in inspection processes and undermined the robustness of GCP inspection, in particular as part of verification of applications for marketing authorizations. The GCP Inspectors Working Group in cooperation with EMA has published a Q&A on this issue.

The challenges of following the advice from the Q&A are related to the fact that:

- Based on experience, most ICFs do not refer explicitly to EU/EEA authorities
- Even if the sponsor confirms that according to his understanding, a more general wording of the ICF would allow EU/EEA authorities to access trial participants' files, this is not sufficiently reassuring evidence for EU/EEA inspectors. This uncertainty impairs the robustness of the

inspection procedure and can negatively affect the timelines of the marketing authorization procedure and data reliability.

- It is not feasible to routinely request for each inspection the opinion of the relevant Independent Ethics Committee (IEC) or Institutional Review Board (IRB) or local regulatory authorities before the conduct of a GCP inspection in a 3rd country. This would also impair the conduct of unannounced inspections.

### **10.1. Proposed solutions – in legislation**

Amend the aforementioned Implementing Regulation to establish inspectors' powers to access trial participants' files in 3rd countries, unless the ICF allows access only to the local competent authorities.

Additionally clarification on sponsors'/applicants' obligation to ensure compliance with European legislation when applying for a marketing authorisation in the EU/EEA (in Regulation (EC) 726/2004) would be helpful (e.g. update Article 17). Regulation (EU) 536/2014 Article 29 Nr. 2.a could be amended to clearly state that participants' data are subject to inspections conducted by the EU/EEA authorities.

### **10.2. Proposed solutions – in guidance**

To further clarify the provisions of the Implementing Regulation (EU) 2017/556 in relation to the inspectors powers during inspections performed in and outside EU/EEA, the Commission Guidance for Applicants regarding Informed Consent could be updated to include a statement that EU inspectors have the authority to review trial participants' medical records and other personal data:

[https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent\\_en.pdf](https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf)

Reference:

[Q&A: Good clinical practice \(GCP\) | European Medicines Agency \(europa.eu\)](#)

## **11. Legal remit of 3rd countries competent authorities to access EU trial participants' documentation during a GCP inspection**

Current situation:

The CTR does not contain provisions regarding the access of 3rd countries competent authorities to EU trial participants' documentation when inspecting sites located within the EEA.

However, there is already national legislation in place, for e.g. in Denmark, which states the following:

"...An informed consent obtained in accordance with chapter V in the regulation provides direct access for foreign regulatory medicines authorities to obtain information in medical records etc., including electronic medical records, with the purpose of accessing information regarding trial participants' health information, which is necessary for the foreign authorities' quality control as part of an application for a marketing authorization application for the medicinal product in question."

( <https://www.retsinformation.dk/eli/lta/2016/620>)

### **11.1. Proposed solutions – in legislation**

Amend the Implementing Regulation (EU) 556/2017 to clarify the remit of 3rd countries competent authorities to access EU trial participants' documentation during a GCP inspection, to ensure a harmonised approach between Member States.

### **11.2. Proposed solutions – in guidance**

The Commission Guidance for Applicants regarding Informed Consent could be updated to include a statement that inspectors from 3rd countries have the authority to review trial participants' medical records and other personal data:

[https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent\\_en.pdf](https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf)

## **12. International cooperation on GCP inspections**

Current challenges:

1. Current national procedures do not allow sharing national IRs with 3rd countries, unless they have CAs in place with that Member State. There is therefore the need to have a harmonized procedure on international cooperation on GCP intelligence information and inspections.
2. Additionally, there are no harmonised requirements to notify NCAs when a foreign authority comes to the EU and performs an inspection, unlike for GMP under the MRA. A requirement for notifications and the possibility for EU Member State GCP inspectors to observe 3<sup>rd</sup> country inspections would facilitate international cooperation, harmonization and best use of resources within the EU network.

### **12.1. Proposed solutions – in legislation**

Establish provisions in the Implementing Regulation (EU) 556/2017 that would require EU clinical trial sites to notify the National Competent Authority of any GCP inspections planned, scheduled, or conducted within their territory by third country authorities, in order to assist Member States to ensure the most efficient use of inspection resources when planning their inspections. (in reference to Article 9 (3.) of the Implementing Regulation).

### **12.2. Proposed solutions – in guidance**

Sharing of GCP inspection reports with 3rd country authorities for CHMP requested GCP inspections

- With countries with CAs in place with EMA: EMA to coordinate the distribution of IRs for EMA-GCP-inspections for CAPs to 3rd countries and vice-versa.
- With countries without CAs in place with EMA: EMA to coordinate the distribution of only the IRs for the sites located in that 3rd country.

## 07. Concept paper for EC on Scope of Centralised Procedure

**Main theme:** Reflection focussed on Annex I of Regulation 726/2004 (mandatory scope) with regard to the need to adapt to technical/scientific progress taking into account lessons learnt from COVID-19, considerations on optional scope can be added.

### DISCLAIMER

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The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic lead	<b><i>Experts from EMA</i></b>
Drafting group	<b>Experts from CHMP, BWP, QWP and EMA</b>

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# 1. Mandatory scope of the centralised procedure

## Problem statement

### ***Medicinal products containing new active substance(s)***

The centralised procedure was introduced in order to ensure a single scientific evaluation with the highest possible standards for innovative and technologically advanced medicinal products. Whilst the access to the centralised procedure was compulsory for some medicinal products, in particular those derived from biotechnology or other advanced technology, it was also possible for applicants to submit a centralised marketing authorisation application on a voluntary basis for medicinal products containing a new active substance.

Throughout the years, the mandatory scope of the centralised procedure has been extended to cover medicinal products containing new active substances in relation to specific therapeutic areas. Different measures have also been introduced at EMA to support innovation such as incentives for SMEs and PRIME.

Nowadays, almost all medicinal products containing a new active substance are submitted through the centralised procedure. For instance only 3 new active substances were approved via MRP/DCP from 2016 to 2020, source: [Heads of Medicines Agencies: Statistics \(hma.eu\)](https://hma.europa.eu/heads-of-medicines-agencies-statistics).

It is therefore recommended to regularise the situation by extending the mandatory scope of the centralised procedure to all medicinal products containing a new active substance.

It will continue building on the regulatory knowledge acquired and ensuring harmonisation within the single market, in particular for products fulfilling an unmet medical need or responding to a pandemic situation.

This will also simplify the operability of the centralised procedure where unclarity regarding the interpretation of point 3 of Annex I or limitations were reported (e.g. 'prevention' of these diseases were excluded).

### ***Update of the eligibility criterion for medicinal products produced by biotechnological means (indent 1)***

Another compulsory access to the centralised procedure relates to the submission of medicinal products developed by means of certain biotechnological processes (recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods). It was reviewed whether the current wording is still up-to-date or whether new innovative technology needs to be captured.

To this effect, the following is recommended:

- The criterion of '*recombinant DNA technology*' is considered appropriate, hence proposed to be maintained.
- For criterion on '*controlled gene expression in prokaryotes / eukaryotes*', it is recommended to maintain the current definition unchanged.
- With regard to the criterion '*hybridoma and monoclonal antibody methods*', the inclusion of hybridoma is considered still appropriate. However, the wording on "monoclonal antibody



techniques" is considered outdated, redundant and should be removed, as recombinant technology and hybridoma already cover monoclonal antibodies technologies.

The Drafting Group is of the view that medicinal products produced by the means of gene editing technologies should be submitted centrally. Gene editing technologies are covered as part of indent 1a concerning 'advanced therapy medicinal products'. In order to ensure that the Gene Therapy Medicinal Products (GTMP) definition is 'future-proof' by including all types of gene editing technologies, the wording of the definition of GTMP is reviewed (reference is made to the discussion on 'gene editing' under the Concept paper 'core definitions').

There were some reflections also whether synthetic nucleic acids (NA)-containing medicinal products should be submitted exclusively centrally. Whilst a centralised evaluation for innovators was considered relevant, this was deemed neither scientifically justified nor proportionate for the evaluation of their copies. As initial applications will be already covered by the indent on 'New Active Substance' and as application under Article 10 of Directive 2001/83/EC do not need to depart from the standard approach for abridged applications laid down in Article 3(3) of Regulation (EC) No 726/2004, a separate indent covering exclusively these substances is not considered adequate. Of note, the optional scope will remain available for applications that do not fall within the mandatory scope and where the applicant is able to demonstrate a significant therapeutic, scientific or technical innovation.

### ***Complex generics***

Currently, generics and hybrids of national products are submitted at national level, whilst generics and hybrid of centralised products can be submitted centrally or nationally upon the choice of the applicant.

Hybrids of national products can access the centralised procedure provided that at least one of the criteria of the optional scope is fulfilled. In addition, those applications must be submitted centrally if they have been orphan designated.

An alternative to the current situation could be to carve out complex generics and include these products in the mandatory scope in order to have a systematic review at centralised level.

However, it should be considered that many applicants developing this category of products are small companies that do not necessarily intend to market in many Member States and could not always assume the higher costs for authorisation and maintenance of the centralised procedure. This might also have some impact on the development of repurposed drugs by industry, not-for-profit organisations and academia.

Rendering compulsory these applications to the centralised procedure may lead to disincentive these developments.

Furthermore, it should also be considered that "complex generics" is a subjective and not well-defined concept, as detailed in concept paper 2 on generics/biosimilars. such concept would be difficult to operate at time of eligibility, creating unnecessary assessment with a risk of divergent interpretations between authorities. The term 'complex generics' is linked mainly with medicinal products where the conventional bioequivalence studies on which to base authorisation, due to the route of administration, complex physico-chemical structures or complicated pharmacokinetic profiles, but it does not match the concept of 10(1) or 10(3) legal basis and therefore it cannot be stated that all hybrids are complex generics. Indeed, hybrid concept currently encompass medicinal products that are equivalent to the reference medicinal products (e.g. topical products that cannot demonstrate equivalence by the means of bioequivalence studies) but also medicinal products that include differences compared to the

reference medicinal product (e.g. new indication, pharmaceutical form, strength, route of administration...). Furthermore, in view of the experience acquired throughout the years on generics, it is proposed to accept as generics (article 10(1)) some medicinal products for which equivalence can be demonstrated based on other studies than bioequivalence (e.g. topical).

Furthermore, abridged applications bringing innovation have the possibility to access the centralised procedure through the optional scope. In addition, the innovative aspect may for some of these developments supports a request for orphan designation and therefore being eligible to the centralised procedure and benefit from dedicated incentives.

In view of the potential impact on the development and market access, the complexity of defining and operate the concept of 'complex generics' and the possibility to already access the centralised procedure for products bringing an innovation, the added value of extending the mandatory scope to these products is not established.

It is therefore proposed not to extend the mandatory scope to include 'complex generics', however it is proposed to better defined in guidance that the criterion of 'significant innovation' for the optional scope could cover innovative products developed on the basis of an abridged application, in particular for repurposed products. Reference is also made to the discussion on 'complex generics' under the concept paper 2 'generics and biosimilars'.

### **Biosimilars**

A biosimilar product produced by means of a biotechnology process referred to in point 1 of Annex I needs to be submitted centrally.

A similar biological medicinal product of a national approved product is required to be submitted nationally, unless it is produced by means of a biotechnology process referred to in point 1 of Annex I or if the applicant can demonstrate that at least one of the criteria of the optional scope is met. The drafting group considered that this approach remains adequate and should not be modified.

Of note, the proposal in the concept paper 2 'generics and biosimilars' proposes to modify Article 10(4) to include the synthetic copy of a biological reference medicinal product.

An alternative to the current situation above described was considered to impose the submissions of all biosimilars to the centralised procedure in order to have a systematic review by CHMP, irrespective that the reference medicinal product is authorised nationally or centrally.

However, this proposal would cover biological substances that are already well known (e.g. allergens, enzymes (such as urokinase, streptokinase), heparins/LMWH, non-recombinant insulins, bacterial lysates) and benefit from the extensive regulatory knowledge acquired on these substances at national level.

As *per* the current practice reflected in Notice to Applicants Chapter I<sup>1</sup>, applications under Article 10 of Directive 2001/83/EC can be submitted nationally if conditions of Article 3(3) of Regulation (EC) No 726/2004 are met. It has also been considered whether all biosimilars of centralised products should be submitted centrally. This is not deemed necessary for biosimilars not produced by the means of

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<sup>1</sup> Notice to Applicants, Chapter I, Volume 2a, rev11: 'Applications on the basis of Article 10, where the reference medicinal products is centrally authorised may be submitted via the centralised procedure. Alternatively, they may be authorised by the competent authorities of the Member States through a national, mutual recognition procedure or decentralised procedure provided that the conditions, laid down in Article 3(3) of the Regulation are met (e.g. same summary of product characteristics, same name in all the Member States). Those Similar biological ("biosimilar") medicinal products which are developed by means of one of the biotechnological processes listed in the Annex to Regulation (EC) No 726/2004 must however be authorised via the centralised procedure'.

innovative technologies, that should follow the same regimen than for generics under Article 3(3) of Regulation (EC) No 726/2004, in order to maximise the options for applicants and therefore market access. Whilst there is a scientific justification that all biosimilars produced by the means of innovative technologies should be reviewed at centralised level, this is not the case for similar biological products not using these complex technologies. In addition, it is noted that biosimilar applications for non-biotechnologically produced substances are limited at national level (e.g. 2 DCP at national level for the period 2018-2020) and at centralised level (2 biosimilars of 86 authorised centrally biosimilars). It is also noted that the number of centrally authorised non-biotechnology produced biologicals is low and the proportion vs. biotechnology produced biologicals will decrease over time.

In view of the above, the added value of extending the mandatory scope of the centralised procedure to all biosimilars or all biosimilars of centralised products is not established. It is therefore proposed to maintain the current situation that allows an adequate repartition in the network of the biosimilars depending on their complexity and the knowledge acquired, as well as centralising at EMA level the evaluation of the most complex biosimilars, i.e. produced by the means of innovative technologies.

### ***Combination products***

Drug-device combination (DDC), either integral, co-packaged or to be used with a medical device referenced to in the product information, are frequently observed in medicinal products. Many of these combinations are not complex (e.g. measuring spoon, syringe) and have been authorised for years in medicinal products (including at national level).

In view of the widespread use of medical devices to be used with medicinal products, the drafting group considered neither effective nor proportionate to mandate the submissions of combination products to the centralised procedure. This would create short term sustainability for the network without adding added value, as in many cases a centralised review would not be justified.

An alternative to focus on a subset of combination products would also lead to subjective criteria difficult to operate at time of eligibility and creating uncertainty for stakeholders. In addition, it may lead to prevent some of these developments as not all operators would be in a position to support the costs of the centralised procedure.

Alternatively, it is rather advised to clarify access for innovative combinations through the optional scope of the centralised procedure (see section 2 on optional scope) and to build on existing platforms of interactions with Member States (e.g. CMDh) to exchange and ensure common approach in the network.

## **1.1 Proposed solutions – in legislation**

It is proposed to extend the mandatory scope of the centralised procedure to medicinal products for human use containing a new active substance, through the amendment of Article 3(2)a and Annex I point 3 of Regulation (EC) No 726/2004.

As for the current Regulation, a cut-off date should remain to ensure stability and coherence. Currently, a medicinal product containing an active substance which, on the day of entry into force of the Regulation (i.e. 20 May 2004) was not authorised in the Union is considered 'new' for the purpose of the eligibility to the centralised procedure. For legal certainty and stability, it should be clarified in the transitional measures of the legislative act that already authorised substances nationally should not be considered as NAS at time of entry force of the revised Regulation.

It should be included in the Directive 2001/83/EC and/or the Regulation (EC) No 726/2004 that homeopathic medicines should be submitted at national level. It is also understood that traditional herbal medicinal products do not have access to the centralised procedure (Article 16b(2) of Directive 2001/83/EC).

Noting that there is heterogeneity in the regulation of allergen products across Member States and a widespread use of products for allergen immunotherapy not covered by a MA (as Named Patient Product (NPP) according to Article 5 of Directive 2001/83/EC) and noting the policy options discussed in concept paper 5 – core definitions, considerations should be given for allergens to be evaluated at national level should a MA be required, unless produced by means of a biotechnological process or the applicant demonstrates eligibility to the optional scope.

Finally, it is proposed to update the biotechnological processes indent referred to under point 1 of Annex I according to the state-of-the-art.

#### Annex I

1. Medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology,
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma

1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

~~2. Medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.~~

3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community, ~~for which the therapeutic indication is the treatment of any of the following diseases:~~

- ~~— acquired immune deficiency syndrome,~~
- ~~— cancer,~~
- ~~— neurodegenerative disorder,~~
- ~~— diabetes, and with effect from 20 May 2008~~
- ~~— auto-immune diseases and other immune dysfunctions,~~
- ~~— viral diseases.~~

~~After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal modifying this point and the Council shall take a decision on that proposal by qualified majority.~~

4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

Article 3(3) of Regulation (EC) No 726/2004 should be amended to remove the term 'generics' in Article 3(3) in order to cover for all other type of applications under Article 10 of Directive 2001/83/EC, without prejudice to points 1, 1a, 1b and 4 of Annex I of Regulation (EC) No 726/2004.

Article 3(3), 3(3)(b) and 3(3)(c) may need also to be amended depending on the selected options for generics of the centralised procedure as described in section 3.

## **1.2 Proposed solutions – in guidance**

EMA to update relevant pre-authorisation guidance.

## **2. Optional Scope**

Applicants have the possibility to access the centralised procedure if their medicinal product brings a significant innovation or that a centralised authorisation would be in the interests of patients at Union level.

Building on the benefits of the centralised procedure to support innovation and ensure a high degree of harmonisation, it is still considered appropriate to allow access to centralised procedure for these medicinal products.

In order to increase the predictability for applicants, it is recommended to mandate the development of a guidance detailing the interpretation of the criteria 'significant therapeutic, scientific or technical innovation' and 'interests of patients at Union level'. This could for instance encompass repurposed medicinal products in order to foster such developments.

The same approach is also suggested for complex generics and Drug-device combination (DDC) products bringing innovation, as the optional scope guidance shall bring clarity on the possibility to access the centralised procedure through the optional scope under scientific or technical innovation for certain medical devices and/or new technology (e.g. artificial intelligence).

### **2.1 Proposed solutions – in legislation**

No change to extend the optional scope is needed based on the proposal made above.

A technical change would be needed that is consequential to the proposal to extend the mandatory scope to all medicinal products containing a new active substance and to remove reference to veterinary medicinal products.

Article 3 of Regulation (EC) No 726/2004:

2. Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

~~(a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or~~

(b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community-Union level.

~~Immunological veterinary medicinal products for the treatment of animal diseases that are subject to Community prophylactic measures may also be granted such authorisation.~~

## **2.2 Proposed solutions – in guidance**

Development of a guidance on the optional scope to clarify the interpretation of the criteria 'significant therapeutic, scientific or technical innovation' and 'interests of patients at Union level', with special focus on:

- Technical innovation for certain medical devices and/or new technology (e.g. artificial intelligence);
- Repurposing of new therapeutic use for an existing medicine/active substance for an indication outside its existing authorised indication(s);
- Complex abridged applications bringing innovation.

## **3. Reflection on generic products of centrally authorised medicinal products**

Applicants for medicinal products referring to a reference medicinal product approved centrally have the choice to submit their application through the centralised procedure or through national procedures.

This provides flexibility for the applicant to select the route of authorisation that is the most suitable to its market strategy. In this regard some applicants might submit their applications through the centralised procedure to benefit from a single scientific evaluation that leads to single Decision effective in all EU/EEA Member States, whilst other might submit through national procedures to target only those countries where they intend to market their products, taking also into account the costs related to these authorisation procedures and their maintenance.

In order to ensure an effective coordination between national and centralised levels, interactions have been established between the EMA and the CMDh (e.g. in exchanging information on relevant safety variations).

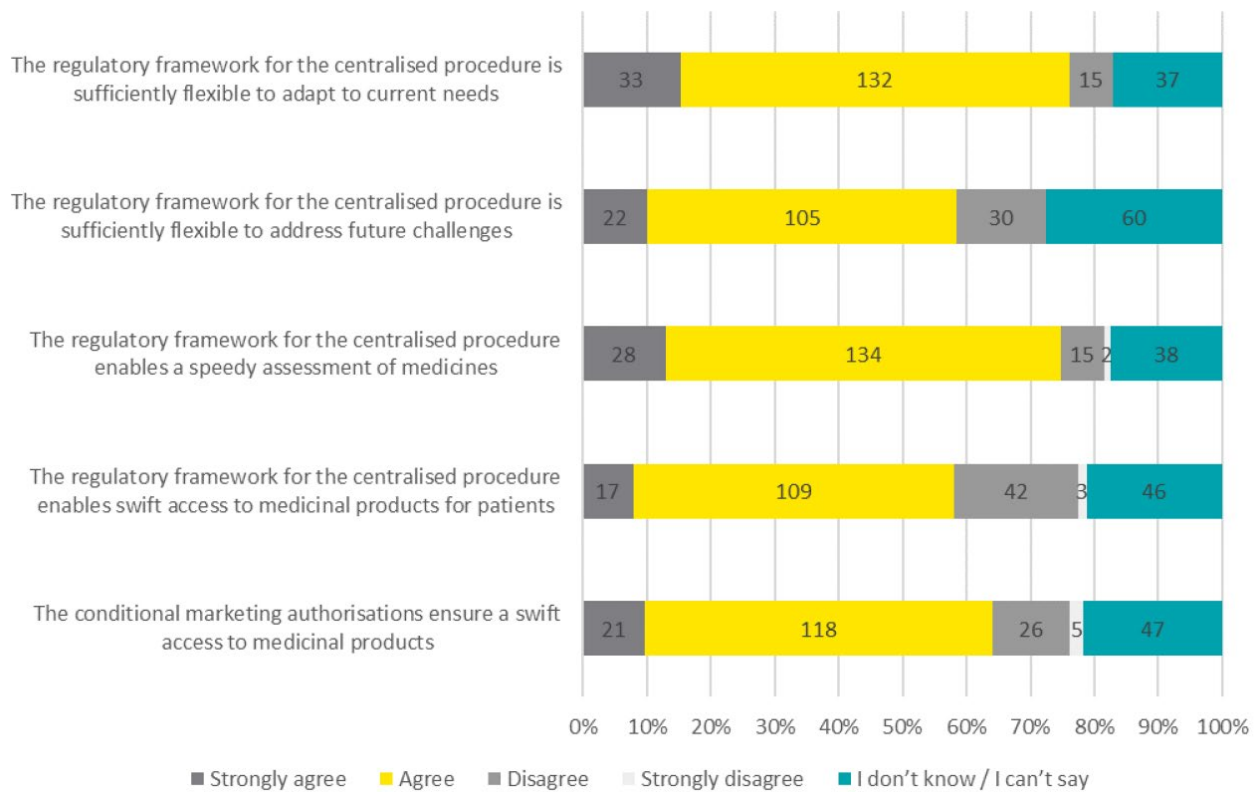
Taking into account the experience accumulated so far in processing these applications, it is proposed to evaluate the following different options as part of the pharma strategy.

### **3.1 Option 1 – Optimise the current situation**

The current framework allows the applicants to choose their preferred route of submission depending on their market strategy and costs for authorisation and maintenance.

Industry stakeholders interviewed as part of the Ernst & Young study for the 10 years report to the Council and Parliament on the performance of the marketing authorisation procedures considered the current scope adequate (86% of responders). They stressed the value of a system that allows choosing the most suitable of the three authorisation procedures (centralised, MRP/DCP or purely national)

depending on the characteristics of the procedure (e.g. timelines, single decision), target markets and, access and maintenance costs.



**Source:** Expert Survey, CMDh Respondents, to the question "To what extent do you agree with the following statements regarding the regulatory framework for the centralised procedure?", Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use European Commission, DG SANTE, Final report January 2020.

The current system leads to the repartition of the workload between national authorities and EMA with coordination achieved through the CMDh and interactions between EMA and CMDh in exchanging key information (e.g. safety information).

Whilst the current framework offers the options for applicants to choose their route of submission, it may need adaptation to ensure the sustainability of the system. For instance, for centralised application, this might be by the expansion of the concept of MNAT or improvement of the single assessment procedure for the Active Substance Master File (ASMF) (reference is made, respectively, to concept paper on functioning of centralised procedure and concept paper on ASMF).

A similar proposal of worksharing procedure could be extended for bioequivalence studies, in order to involve more Member States in the assessment of such studies, which could be adopted in future applications both for centralised and national procedures (reference to the concept paper on Generics and Biosimilars).

In addition, it needs to be determined if there is some benefit for CHMP to continue to be exposed to all possible types of marketing authorisations in the EU or if it should rather focus on specific type of applications/products.

### **3.2 Option 2 - ALL generic products of centrally authorized products must be assessed nationally, with the exceptions of complex generics and biosimilars**

An alternative to the current situation could be a specialisation of the authorities to certain types of applications. EMA could for instance be in charge of assessing most innovative medicinal products whilst NCA would be in charge of generics.

This model would concentrate the expertise for assessing generics at NCAs level, building on a well-functioning system with large experience overseen by CMDh and focus the CHMP expertise on specific products rather than all types of applications.

As it would introduce a systematic disconnect between the knowledge on the centralised reference product and its generics, an efficient system of exchange of information/knowledge should be ensured.

The applicants being not able to choose anymore their routes of authorisation, this option might need to be tested to investigate the consequences to not be able to access the centralised procedure anymore.

In addition, challenging the European Commission's decisions and CHMP scientific assessments by lodging a judicial complaint at central level, i.e. with the General Court in Luxembourg, is a relatively cheap activity compared with the cost of litigations that generic manufacturers would bear at national level if they were to launch proceedings in several jurisdictions. It would ensure an important reward if the complaint were upheld (the judgments issued by the Union Courts would be immediately applicable in the whole Union, as opposed to national Courts' rulings).

There has been indeed a sharp increase of the litigation rate in relation to generic applications filed with EMA in the years 2018-2021, and a consequential increase of the very time-consuming activities required to cope with the judicial proceedings, both at European Commission/EMA Secretariat's and scientific committees' level. In this framework, an indirect advantage of introducing a mandatory decentralised procedure for "simple generics" could be a reduction of the generic manufacturers' tendency to easily use or abuse the judicial route in order to contest a scientific assessment by the CHMP on the relevant reference product, and/or on the merits of their own applications.

### **3.3 Option 3: ALL generic products with reference product approved centrally must be assessed in CP**

Another alternative could be that the generics of centralised procedure shall be submitted centrally.

This option is not recommended as it would lead to losing the flexibility for applicants to adapt their regulatory strategy and leading potentially to some impact on market access. Some applicants might not be able to assume the costs of a centralised marketing authorisation or these costs might not be proportionate to their intended market strategy.

It would also lead to an increasing number of applications over the years to the centralised procedure which puts into question the sustainability of such model for the network.

This option was not favoured neither by the drafting group, nor by CHMP.

Options 2 and 3 would require an amendment of article 3(3) of the Regulation (EC) No 726/2004.



## **4. Additional considerations**

Technical amendments in the legislation might be considered:

- Removing the provisions regarding veterinary medicinal products.
- Consolidating the optional scope with Regulation (EC) No 1901/2006.

## 08. Concept paper for EC on **RWE including registries**

**Main theme:** Future proofing taking into account the better use of RWE and registries – Considerations on main elements and business processes that may need to be reflected in the regulatory framework.

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Topic lead	Experts from EMA
Drafting Group	Experts from CHMP, CAT, PRAC, HMA/EMA Big Data Steering Group and EMA

## 1. Recommendations for change

### Problem statement

- The current pharmaceutical legislation focuses on clinical evidence generated through traditional randomised clinical trials (RCTs). Advances in technologies and methodologies and availability of real-world data (RWD) have prompted a need to allow for broader range of study designs and data sources to inform decision making.
- With regard to the marketing authorisation approval, the current pharmaceutical legislation was written at a time when RCTs were the principal source of clinical evidence when assessing the benefit-risk of a medicine. RCTs are still considered the gold standard in terms of the primary demonstration of efficacy, however, there are specific situations where regulatory questions benefit from complementary approaches such as real-world evidence (RWE). Additionally, RCTs provide evidence under controlled conditions in a relatively small number of selected patients and for a limited length of time and therefore there are situations where observation studies that use RWD are important for addressing specific research questions.
- In the product lifecycle, the use of RWD and RWE including registries in regulatory decision-making has been focused mainly on safety, disease epidemiology and drug utilisation, whereas their place for other areas of use, notably the demonstration of efficacy has been more limited.

- The use of RWE in the development, authorisation and monitoring of medicinal products is increasing, and additionally, the creation and development of the European Health Data Space (EHDS) will further catalyse the availability and use of healthcare data and create new opportunities for the use of RWD and RWE along the medicine's lifecycle. It is therefore proposed to enhance the regulatory framework to further enable the use of RWE.

### Objectives

- An optimal regulatory framework for medicines in the EU should:
  - Recognise, enable, and value the spectrum of data and information sources (explicitly including RWD and RWE) to improve the evidence for regulatory decision-making for the benefit of patients and healthcare systems
  - Define key concepts
  - Provide adequate legal provisions that clearly define roles and circumstances of the use of RWE as supporting tools in decision making on marketing authorisations and the monitoring of the safety of medicines.<sup>1</sup>

## 2. Proposed solutions

It is recommended that the legislation is made future-proof by avoiding inclusion in the main directive and regulation of detailed technical provisions that may become out of date as technology and science progress (the legal text should be technology neutral). Detailed technical provisions should be included in implementing texts and the most rapidly evolving issues should be included in guidance which can rapidly be updated.

The proposals are organised into definitions, provisions which apply to all types of RWD/RWE including registries, registry specific provisions and additional considerations on guidance.

### 2.1. RWE/RWD definitions

- It is recommended that core terms and definitions relevant to RWD/RWE are included in legislation. A non-exhaustive list of terms with proposed definitions is provided below:
  - **Real world data**<sup>2</sup>  
Definition: Routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials.
  - **Real world evidence**<sup>2</sup>  
Definition: Real-world evidence (RWE) is defined as the information derived from analysis of real-world data.
  - **Patient registry**<sup>3</sup>  
Definition: Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. The term 'patient' highlights the focus of the registry on health information. Such registry may include patients with a certain disease (i.e. disease registry), pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature.
  - **Disease Registry**<sup>4</sup>

<sup>1</sup> Ensure that the use of RWE is conducted in accordance with the applicable law on data protection and in respect of the principles relating to the processing of personal data (as per Art 4 of the EUDPR and Art 5 of the GDPR) including the need to safeguard the rights and freedoms of data subjects.

<sup>2</sup> Cave A, Kurz X, Arlett P. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clin Pharmacol Ther. 2019 Jul;106(1):36-39. doi: 10.1002/cpt.1426. Epub 2019 Apr 10. PMID: 30970161; PMCID: PMC6617710.

<sup>3</sup> From EMA Guideline on registry-based studies, 22 October 2021 (EMA/426390/2021)

<sup>4</sup> Adapted from EMA Guideline on registry-based studies, 22 October 2021 (EMA/426390/2021)

Definition: Subcategory of patient registry whose members are defined by a particular disease or disease-related patient characteristic regardless of exposure to any medicinal product, other treatment, or particular health service.

- **Registry based study**<sup>5</sup>

Definition: Investigation of a research question using the data collection infrastructure or patient population of one or several patient registries.

A registry-based study is either a clinical trial or a non-interventional study as defined in Article 2 of Regulation (EU) No 536/2014. A registry-based study may apply primary data collection in addition to secondary use of the existing data in the registry.

- **Registry based randomised controlled clinical trials**<sup>6</sup>

Definition: Registry-based randomised controlled trials use registries as a platform for case records, data collection, randomization, and follow-up.

- **Normal clinical practice**<sup>7</sup>

The Clinical Trials Regulation defines normal clinical practice as ‘the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder’. In the context of observational studies, existing pharmacovigilance guidelines describe ‘diagnostic or monitoring procedures in addition to normal clinical practice’. The drafting group considers that providing a definition of normal clinical practice in legislation would be helpful, including, elaborating that “diagnostic or monitoring procedures in addition to normal clinical practice means procedures that are not performed amongst health professionals including in specialist care or included in clinical guidelines”.

## **2.2. RWD/RWE (including registries)**

- Legislation should include an explicit reference to medicines regulators needing to use RWD to support the development, authorisation and supervision of medicines. This would provide the legal basis for regulators to have access to RWD for studies and routine surveillance. It would simplify access to RWD in the short term but also in the longer-term with the introduction of the EHDS. In Annex I,<sup>8</sup> Danish members of the drafting group provide an explanation of national challenges that could be resolved with the simple addition of an explicit legal basis for broad regulatory use.
- The drafting group considered that it was key to ensure strong legal basis for decision making based on RWE. Under the current legislation, the competent authorities make decisions on the basis of evidence submitted by the applicants/marketing authorisation holders (MAH), with reference to Chapter 3, Article 19 of Directive 2001/83/EEC. In order to further inform decision-making, and to resolve existing doubts on the ability to take regulatory action, an explicit legal basis should be introduced for regulators to consider and decide upon additional evidence available including those derived independently from the applicant or marketing authorisation holder. The need for procedural vehicle may need to be considered. Finally, the Commission may consider that this principle could be applied to additional data sources e.g. preclinical studies or academic clinical trials.
- RWE enabling provisions should be included in the legal framework. Current legislation includes explicit provisions for post-authorisation studies which will often be observational and therefore generally include RWD. However, Annex I of Directive 2001/83/EC (as subsequently amended) is not explicit on the possibility to use RWD/RWE to support marketing authorisation, and lifecycle applications. It is therefore proposed that legislation explicitly recognises the use of RWD/RWE. This could be embedded in the body of the Directive and might also be relevant for its Annex I.
- A current lack of an explicit legal basis for regulators to initiate and conduct RWE studies weakens the justification for such studies and may lead to questions being asked regarding the authority to take regulatory action based on the results. Additionally, an explicit legal basis provides clarity in terms of data processing (data protection). Therefore, there is a need to strengthen the legal bases for the conduct and use of independent RWD studies by National Competent Authorities (NCAs) and European Medicines Agency (EMA), e.g., conduct of data analyses using databases or

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<sup>5</sup> From EMA Guideline on registry-based studies, 22 October 2021 (EMA/426390/2021)

<sup>6</sup> From <https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-018-0836-0.pdf>

<sup>7</sup> From Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

<sup>8</sup> Annex I: Danish experiences regarding legal challenges in use of RWE

independent registries. This legal basis for regulators and potentially downstream decision makers (Health Technology Assessment bodies (HTA) and payers) would enable to initiate, manage and analyse healthcare data to support the decision-making process. This would also provide the basis for direct and rapid access to such data through the EHDS.

Furthermore, the European Medicines Regulatory Network is currently establishing a framework for access to and capability for analysis of RWD (e.g., through DARWIN EU). Further strengthening the legal basis for such data use including access and analysis thereof, building on the Health Union text (mandate for EMA in crisis preparedness and response) is important to cover the full spectrum of regulatory use cases.

- There should be a requirement for mandatory registration of non-interventional / registry-based studies in the EU PAS Register including all post-authorisation studies included in the Risk Management Plan (categories 1, 2 and 3) (as also suggested in Concept Paper 13); such mandate should include the uploading of the study protocol before data collection or extraction and of the final study report. It should be noted that this would be a transparency measure akin to the public portals for clinical trials and not the formal submission for the regulatory assessment as part of eCTD. In addition this will improve study practice by allowing to verify if the study results have been generated according to the planned study design and analysis. This would build on the existing successful but largely voluntary registration of observation studies in the EU PAS register. The processes in place in the EU PAS Register and the possibility to redact confidential information in the study protocol as currently provided to by the GVP Module VIII for post-authorisation safety studies allow the uploading of study protocols before the study is completed.
- As proposed under a separate concept paper<sup>9</sup> the legislation should also be revised to strengthen the legal basis for the submission of (raw) data irrespective of format for potential analysis by the regulators with pseudonymisation measures to be applied and including for secondary use. It is suggested to maintain flexibility as to whether such submission is routine or ad-hoc as this will be informed by the 2022 Committee for Medicinal Products for Human Use (CHMP) pilot on raw data from clinical trials. This may allow verification of analyses comparison across the studies and detection of data irregularities.

Because results from independent studies may impact the benefit-risk of an authorised medicinal product, the legislation should include an obligation for medicines regulators to develop and implement a process for receiving such impactful study results. This process should ensure the confidentiality of the data and the right to publish of the study investigators. An obligation should be introduced on study investigators to submit study results in response to a request from the regulator.

- The drafting group considers that the legislation should provide a legal basis for EMA to certify /qualify RWD sources as this would drive up the quality and utility of such data for regulatory decision making. Options (which could be implemented through guidance) might include formal qualification e.g., through the Scientific Advice Working Party (SAWP), independent audit against published standards (included in implementing acts), or self-certification against published standards. Establishment of a an official RWD catalogue including such certification would enable findability of data (FAIR data principles).
- It is recommended to include a legal basis for the adoption of implementing acts<sup>10</sup> (+/- guidance) to establish as a minimum:
  - Data standards
  - Real world meta-data
  - Data quality framework relevant to RWD and RWE
  - Roles and responsibilities of the actors involved in the processing of RWD and generation of RWE based on the data sources that will be put in place/utilised
  - Requirement for a catalogue of real-world data sources and metadata.

Note 1: Data protection should be an explicit element in any legislative proposal taking into account the sensitive nature of the personal data to be processed. This should include a clear reference to the use of pseudonymisation measures. More specifically, the pharmaceutical legislation should include explicit provisions for EMA and Member States to be able to process

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<sup>9</sup> CP n. 11 on the functioning of the centralised procedure

<sup>10</sup> It is acknowledged that the EDPS under Article 42(2) EUDPR is to be consulted when such legislative proposals will be made

RWD, including registry data, to generate RWE for regulatory assessment and decision-making. Such explicit provisions should also serve as the basis for the compatible and lawful further processing (secondary use) of personal data (as per Art 5 and Art 10 of the EUDPR and Art 6 and Art 9 of the GDPR).

Note 2: Some members of the drafting group suggested that, considering the additional activities foreseen, additional funding either from the Community budget or from fees charged to applicants/MAHs is required to fund public health efforts linked to RWD/RWE in decision making.

Note 3: Some members of the drafting group considered that the legal bases for pre-authorisation use of medicines needs clarification<sup>11</sup>.

### **2.3. Registries**

- As with the driving principles of this paper it is suggested that for registries definitions, principles and key obligations are included in legislation with details in implementing texts and guidelines.
- Obligations and principles for registry data collection and sharing for regulatory purposes could have a very positive impact on evidence generation and regulatory decision making. It was acknowledged that under the current framework the pharma legislation does not place obligations beyond regulators and applicants/marketing authorisation holders.

The drafting group was split on whether to extend obligations to include all registry holders. Part of the group was in favour of obligations also for non-MAH registry holders, while others were concerned that such obligations could be in conflict with patient consent, purpose of the registry or national legislation. This could lead to opt-out, lowered data quality and reduce willingness of undertaking good registry follow-up. The Commission therefore needs to consider which obligations for registries in the legislation could be applicable to all registry holders, and which should be applicable only to MAHs. Beyond core obligations like registration of studies and sharing of results, further details on good data/registry practice, including data sharing, would be expected in implementing texts. Concrete proposals could be provided by the drafting group in the subsequent iterations of the RWE concept paper.

- When they are used to generate RWE, sources of RWD funded or managed by applicants/MAHs (e.g., registries, electronic health records, epidemiological data, case series, data from other non-interventional studies or surveys) should be required to apply pseudonymisation measures and allow pseudonymised data and metadata to be shared with regulators.
- There would be benefits to providing a legal basis for the European Reference Networks (ERN) to establish tools that support the establishment and maintenance of high-quality registries and enable the linking and collation of pseudonymised patient data and meta-data to support analysis and generation of evidence. Tools might include templates, core data elements, certification / qualification (this may include certification of registries to facilitate multi product use), or IT tools (the Union could consider provision of platforms for registries e.g., by Joint Research Centre (JRC), EMA or as part of EHDS).
- A legal basis should be provided to require MAHs to join a registry-based study or data collection scheme that might be pre-existing, either sponsored by other MAH(s) or being publicly funded (e.g., in case of studies/registries relevant to the class or disease or in case of studies being already ongoing as requirement when generics enter the market). A reciprocal obligation for MA holders holding a registry-based study to include additional products should be included.
- As a guiding principle, the new legal framework should enable better engagement from patients in RWE/RWD and strengthen the possibility of patients' direct data entry into registries.

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<sup>11</sup> It shall be stated in future regulations that RWD collected before market approval of a medicinal product presupposes that the use of the drug takes place on a legal basis, for example a special permission (e.g., under Article 5(3) of the (Regulation (EC) No 726/2004), Compassionate use (under Article 83 (1) of Regulation (EC) No 726/2004) or a Hospital exemption (under Article 28(2) of Regulation (EC) No 1394/2007).

## **2.4. Additional considerations for implementing texts / guidance**

Guidance is needed on (non-exhaustive list):

- The place of RWE in regulatory decision-making (evidentiary value). This would be drafted over time and evolve as regulatory science moves on. It is important that such provisions are not included in the basic legislation in view of this evolution and the fact that evidentiary value will be use-case specific.
- Formal EU RWE methodological guidance to complement guidance on evidentiary value and building on the existing (but as yet without regulatory status) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methods guide.
- Good data practices for registries and different sources of RWD to ensure appropriate standards. They should cover, inter-alia, governance attributes e.g., for harmonisation of data collection and management process, data entry and changes to registry data, implementation of audit trail, data management and archiving for closing registries, capacity to verify and clean data, core data elements to be collected (e.g., on medicinal products), data standards/format principles, standardised data dictionaries and minimum analysis sets to facilitate standardisation and use of registry data for regulatory purposes as well as reporting/transparency.
- Metadata, digital identity and meeting FAIR principles of findability, accessibility, interoperability, and reusability.
- Modalities for sharing of data with regulators where needed to inform the evaluation and supervision of medicinal products and between different parties for research purposes, or data related to major public health issues outside specific regulatory procedures.
- Best practices to collaborate and establish joint database/platform between national patient or disease registries.
- Use of RWE in special populations.
- Recommendation for feasibility analysis (e.g., to follow the format included in the Guideline for registry-based studies for other sources of RWD).
- Considerations and principles related to RWD/RWE recommended for scientific advice.
- Data quality with a legal basis for applying a data quality framework.
- Options for formal qualification e.g., through SAWP, independent audit against published standards (included in implementing acts), or self-certification against published standards.
- Roles and responsibilities of the actors involved in the processing of RWD based on the data sources that will be put in place/utilised.
- Catalogue of real-world data sources and metadata.

# Annex I

## Danish experiences regarding legal challenges in use of RWE

### I. Proposal

For the purposes of analysis of RWD conducted by medicines regulators seem to fall between two chairs: administrative use and research. The current solutions to this problem encompass anonymization of data, stretching the definition of research, conjure legal basis for analysis on an ad hoc basis or pay research institutions. However, all of these solutions have efficiency, quality and/or economic downsides. Ensuring a solid, legitimate and transparent legal basis will also be an important precondition for realizing the ambitions, potential and basic functionality of EU initiatives such as DARWIN EU and European Health Data Space.

An EU wide regulation defining the processes to be driven by evidence in public institutions such as NCAs and EMA in the form of statistics and research, would create a solid basis for efficient utilization of healthcare data.

### II. Background

Many health registries are created for specific purposes such as administrative use, quality control and research purpose. Examples of such registries in a Danish context are electronic health data records (EHR), oncology registries and patient- and prescription registries.<sup>12</sup> Generally, such registries can be used for research purposes, while use of the data for administrative purposes by authorities require a specific legal basis or consent from the data subjects.

This distinction between administrative and research uses ensures on the one hand, the freedom of researchers to pursue the generation of new knowledge, on the other hand, transparency in the basis on which authorities makes regulatory decisions to safeguard fundamental rights of the data subjects.

Statistical analysis on data from specific purpose registries is a powerful and efficient tool to inform regulatory and political decision making. This is a process that is significantly different from routine use of data for administrative decision making. The complex issues to be analyzed require the freedom of method that is characteristic for research. On the other hand, the purpose is not research but specifically to inform political and/or regulatory strategic decision making that will affect e.g., industry and by implication individuals. For example, an analysis observing an increased use of opioids could be used *strategically* by regulatory authorities to initiate a communication initiative or issue stricter guidelines for prescription. Or *administratively* to identify and sanction specific doctors prescribing more opioids than average.

If statistical analysis is considered an administrative purpose, a clear, specific, and unambiguous legal basis is needed to process the data. This would leave very little flexibility in the design and conduct of the analysis. On the other hand, categorizing the statistical analysis as research to get the freedom of method enshrined in this category stretch the concept of "research" very far and potentially undermine the boundaries between research and authorities to the detriment of the legitimacy of both.

Hence, in Denmark, *researchers* may conduct studies using health data from specific purpose registries and other data to e.g., make recommendation on societal and political decision making, assess correlation between diseases, suggest better treatment or scrutinize the organization of healthcare institutions<sup>13</sup>. But *public institutions* themselves cannot unless they have a specific legal basis to conduct such studies or are also designated as a research institution. This latter option is only used in

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<sup>12</sup> See the Danish Health Data Authority for lists of Danish health data registries: [English - Sundhedsdatastyrelsen](#) (last accessed 23.02.2022)

<sup>13</sup> These examples are taken from ministry of health report on health research in danish registries from 2021, <https://sum.dk/Media/637614378090066298/Registerdata%20i%20Dansk%20Sundhedsforskning.pdf>



very specific domains, e.g., the Danish Serum Institute which is a research institute also undertaking public duties such as procurement of vaccines.<sup>14</sup>

The current situation in Denmark is, that the legal foundation for use of data from health data registries by public institutions for statistical analysis is non-existing or at best ambiguous and ill-defined. Simply speaking, it falls between the categories of administrative use (i.e., for making a decision in relation to an individual citizen) and research.

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<sup>14</sup> <https://en.ssi.dk/about-us>

## 9. Concept paper on environmental challenges

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Drafting lead: Experts in the Pharmaceutical Committee ad-hoc Working Group on pharmaceuticals in the environment

### Introduction

Following the adoption of the pharmaceutical Strategy for Europe<sup>1</sup> that also sets flagship actions to address the environmental challenges, the ad-hoc Working Group on pharmaceuticals in the environment (PiE WG) was also given the task to draft a concept paper on the environmental challenges. The scope of this paper are human pharmaceuticals.

To accomplish this task, the WG set up a concept paper group that was joined by experts from EMA and nine Member States: Austria, Czech Republic, Finland, Germany, Italy, Slovenia, Spain, Sweden, and The Netherlands.

This concept paper is outlining the technical expert views that are solutions oriented to bring the necessary support in the revision of the EU pharmaceutical legislation (Directive 2001/83/EC) and as considerations on main elements and business processes that may need to be reflected in the regulatory framework on the following aspects:

- Strengthening the environmental risk assessment (ERA) requirements and conditions of use for medicines and take stock of the results of research under the innovative medicines initiative;
- Greener pharmaceuticals with respect to antimicrobial resistance. For this point, the WG also consulted the EMA Good Manufacturing and Distribution Practices (GMDP) Inspectors working group on the aspect relevant to manufacturing of active substances and finished medicinal products and GMDP and reflected their input in the finalised concept paper.

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<sup>1</sup> COM(2020) 761 final, 25.11.2020, <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN>

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## **1. Strengthening the environmental risk assessment requirements and conditions of use for medicines and take stock of the results of research under the innovative medicines initiative**

We report on this in three separate chapters: Chapter 1.1 on strengthening the requirements of the environmental risk assessment, Chapter 1.2 on conditions of use, and Chapter 1.3 on the results of research under the innovative medicines initiative.

### **1.1 Strengthening the environmental risk assessment requirements**

#### **1.1.1 Current situation**

In the current Directive 2001/83/EC the risks related to use of a medicinal product (for human use) include any risk of undesirable effects on the environment, as set in Article 1 point 28.

As per Article 8(3)(ca) of Directive 2001/83/EC, an environmental risk assessment (ERA) is required to be submitted as part of any marketing authorisation application. The requirement for an ERA applies regardless of the legal basis chosen by the applicant, since no derogation of this requirement is laid down in Article 10 of that Directive.

This ERA should be carried out in accordance with point 1.6 of Annex I to that Directive: “*Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.*”

However, as set in Article 1 point 28a of that Directive, ERA is not part of the Benefit/Risk (B/R) balance that is performed as part of the evaluation of medicinal products for human use. As a consequence, based on the current legal provisions (Article 12 of Regulation (EC) 726/2004 for centralised procedure, and Articles 26 and 21a of Directive 2001/83/EC respectively), an unsatisfactory/incomplete ERA is neither a ground for refusal of a marketing authorisation nor can be imposed as a condition to the marketing authorisation; it could only be requested to be completed post-authorisation as a recommendation.

Other legal requirements relevant from the environmental viewpoint are limited to the disposal of unused or expired medicinal products, including requirements for labelling of specific precautions and reference to appropriate collection system that Member States shall ensure (Articles 54j and 127b of Directive 2001/83/EC).

Regulation (EC) No 726/2004 for centrally authorised products provides for similar provisions related to the ERA: e.g., Article 6 for the reference to the particulars of a marketing authorisation application. Except for Article 20(4) of Regulation (EC) No 726/2004 which allows for urgent actions to be taken to protect the environment, Directive 2001/83/EC only justifies it on public health grounds. Those ERA requirements are further developed in the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 21 \*)

This first part of the paper is related to the aspects of the ERA, however, there may be links related to the second part dealing with manufacturing aspects of the medicines.

#### **1.1.2 Issues and solutions**

In this section, the various issues identified earlier (e.g. in the EU’s Strategic Approach on Pharmaceuticals in the Environment, documents to prepare stakeholder workshops and the results of these workshops, and a workshop held by the Pharmaceutical Committee in April

2021) will be briefly described from the viewpoint of the experts. Following this short-list, the issues are analysed in more detail, working towards practical solutions.

***Adverse environmental impacts due to the use of pharmaceuticals should be minimised, without affecting availability for patients. This should be achieved by making studies judged as being necessary for the ERA (according to the ERA guideline) mandatory, by raising an unsatisfactory ERA as a major objection. The backbone of all proposed changes is that environmental impacts due to the use of pharmaceutical products should be transparent, publicly available and mitigated.***

A number of issues currently hinder this:

- > The legislation is unclear on what constitutes an ERA and which are protection goals;
- > The ERA does not include the protection of human health via the environment;
- > There is no provision to enforce the completion of the necessary ERA studies;
- > Apart from the general statements in the labelling, specific risk mitigation measures cannot be forced in case an environmental impact has been shown in the Environmental Risk Assessment (ERA);
- > For substances with a predicted environmental impact, it is not required to provide consumption data following authorisation and to monitor their presence in environmental compartments;
- > Pharmaceutical and environmental legislations are not coupled;
- > The ERA is product-based, different dossiers with different data and subsequently different conclusions exist for similar medicinal products with the same active substance; the evaluation of excipients is not included except for specific reasons;
- > ERA data are often not publicly available, and difficult to find by stakeholders;
- > No ERA has been performed for legacy products (authorised before 2006);
- > There is no regular re-evaluation of the ERA based on new scientific information or monitoring data environmental frameworks, particularly for active substances with a risk;
- > There is no monograph system or general database for environmental data for active substances or environmentally relevant excipients, like for other chemicals frameworks;
- > Data are not shared between Marketing Authorisation Holders (MAH), which leads to unnecessary repetition of studies. This is particularly relevant for in vivo fish studies, which should comply with the 3R principles established in EU DIR 2010/63 intended to reduce animal testing;
- > The ERA reports are not always of good quality due to a lack of environmental expertise in Member States; this also leads to a lack of harmonisation in the assessment where different conclusions may be reached for similar medicinal products with the same active substance;
- > There is no central ERA Working Party for human pharmaceuticals at EMA;
- > Limit values for emissions of active substances due to production are not available.

These issues are discussed below in more detail with their solutions.

#### **1.1.1.1 Clarifying the scope of the ERA and protection goals**

##### ***Problem statement***

In Part 1 (standardised marketing authorisation dossier requirements) of Annex I of the consolidated text of Directive 2001/83/EC, the only text which applies to ERA performed for non-GMO medicinal products is the following:

*Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions (section 1.6 of the Annex I to Directive 2001/83).*

This succinct text is vague and thus leaves room for interpretation. Although the guideline on the environmental risk assessment of human medicinal products<sup>2</sup> has been developed, this is not a legally binding document and therefore the principles of ERA described in the guideline should be underpinned by legislation, which is currently not the case. The requirements for non-GMO ERA and GMO ERA sections are not clearly separated in Annex I although the principles underlying the assessments are very different: for GMO ERA they are much more detailed.

The current legislation is silent on risks for Anti Microbial Resistance (AMR) and other risks to humans due to exposure to pharmaceutical residues via the environment. At the moment, the ERA aims to protect exclusively ecosystems. In the EU Strategic approach to PiE, the link between residues of pharmaceuticals present in the environment and the impact on human health is addressed as a challenge in an own chapter. Pharmaceutical residues are found ubiquitous in various environmental compartments and also in wildlife organisms and may pose a threat to human health via drinking water, fish consumption, irrigation of crops with treated wastewater, application of sludge as fertilizer on agricultural soils, etc. A specific challenge is the development of AMR and the presence of antibiotic residues, e.g. in soil or surface water and raw water resources for drinking water use. The current legislation does not address health threats via the environment as part of the safety assessment and this need to be included in the ERA.

Besides this, human health issues also arise during manufacturing, especially for antimicrobial products. There is a link between this issue and part II of the concept paper on greener production of antimicrobial products. Various scientific reports have shown very high concentrations of antimicrobials and AMR close to production sites. This is a threat to human health.

Art. 8.3 of the Directive 2001/83 refers to “medicinal product” when describing the evaluation of the potential environmental risks. Current EMA ERA guideline also refers to “medicinal product” but the Q&A document<sup>3</sup> indicates that “the applicability to the ERA should be considered regarding the active ingredients of pharmaceuticals” (Q12). EMA ERA guideline under revision indicates that the focus of ERA is the active ingredient and that “Excipients do not generally require an ERA unless there is a specific toxicological effect to suggest an environmental risk under the product’s conditions of use.”

### ***Legislative solutions***

To amend Annex I of Directive 2001/83/EC to:

1. Clearly define the scope of the ERA. The ERA should assess the risks and hazards related to the active substance, but also related to excipients which are emitted to the environment during or after use and have a specific toxicological effect or biological activity (e.g. antioxidants), or other environmental issues (e.g. chlorofluorocarbons)<sup>4</sup>.

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<sup>2</sup> <https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use>

<sup>3</sup> [https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf)

<sup>4</sup> Note that currently the definition of “finished product” is missing in the Directive; this also relates to the scope of the ERA and thus should be added. Also note that currently the

2. Include in the scope of the ERA the possibility to derive emission limit values for the active substance if these are needed for manufacturing guidelines (e.g., for antimicrobials (see section 2). These should be based on the same data as already available for the ERA. Besides this, the emission limits could also be based on data to prevent risks due to AMR, if relevant. A catching-up procedure may be needed to obtain emission limit values for legacy products.
3. Include risks to human health via the environment as a protection goal. The issue of public health risks due to exposure via the environment (“One Health Approach”) should be considered to be mentioned in the new legislation as part of the definition of the risks related to the use of the medicinal products (Article 1(28) as proposed below):

28. Risks related to use of the medicinal product:

- any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;
- any risk of undesirable effects on the environment;
- any risks of undesirable effects on public health, including anti-microbial resistance and exposure of humans via the environment.

and in the Annex of Directive 2001/83/EC at the appropriate points also in Part II, Part III (e. g. vaccines), and Part IV (advanced therapy products).

4. Separate more clearly non-GMO and GMO ERA requirements and add a greater level of detail to the ERA dossier requirements for non-GMO derived medicinal products including the principles of ERA (e.g., a tiered hazard and risk assessment, protection goals, chemical and biological risks (including AMR) with appropriate definitions).
5. Clearly state that the ERA should follow the EMA Guideline (EMEA/CHMP/SWP/4447/00 corr 21 \* )
6. Add a section on product-specific requirements for risk mitigation, especially for products with an estimated risk.

### ***Solutions on a guideline level***

- The guideline on ERA would need to be further revised to be in line with (new) protection goals. Most scientific methods to assess the risks related to these protection goals have already been developed in other regulatory frameworks and would only need to be slightly adapted for use in pharmaceutical ERA.
- The environment is a reservoir and vector for AMR. Although there are still knowledge gaps in terms of potential risks to human health due to the spread of resistant bacteria via the environment, measures should be taken to reduce the exposure of the environment to antimicrobials for precautionary reasons. The assessment of potential risks of AMR development and maintenance in the environment should be included in the dossier requirements for antibiotics and antimicrobials.
- The methodology for assessment of medicinal product residues in groundwater and surface water used as raw water for drinking water, in surface water used for recreational purposes or for fishing, or in wastewater / sludge used for irrigation / fertilization of fields, should be developed in a dedicated guideline. Risk management should be strengthened for substance for which their use is identified to pose a risk.

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introduction of “functional excipients” in legislation is under discussion in other concept papers.

- Methodology on how to derive emission limit values and where and when to apply those should preferably be developed together with existing legislative frameworks.

***Additional remark by the group***

It should be further investigated whether integrated sustainability concepts (e.g., impact of manufacturing of active substances on the environment, green/clean pharmaceutical chemistry) could also be part of the ERA. Interplay with environment legislation and, if emission limit values are included (See part 2 of this paper), good manufacturing practice (GMP) would be necessary. Moreover, a guideline could be developed on how to weigh environmental impact (including other sustainability aspects) in order to compare different active substances and/or products, e.g., to be used for sustainable procurement. This would be in line with the recently published EU Commission’s ‘Recommendation on the use of Environmental Footprint Methods’<sup>5</sup>.

**1.1.1.2 Enforcing a complete ERA prior to authorisation**

***Problem statement***

A complete and timely ERA is needed at the time of marketing authorisation to decide on appropriate mandatory risk mitigation measures. Currently, when the ERA is incomplete at the time of marketing authorisation, the missing information is requested to be provided post-authorisation as a non-binding recommendation/commitment. Although the majority of Applicants under the centralised procedure fulfil their obligations with regards to ERA at time of CHMP opinion, this is often not the case at national level, especially in decentralised procedures. Furthermore, to avoid delaying a marketing authorisation, it is common practice under the decentralised procedure that ERA outstanding concerns are not further pursued if it is anticipated that an agreement between the reporting Reference Member State (RMS) and the Applicant will not be reached before end of the procedure.

Although the ERA is part of all marketing authorisation applications (listed in Article 8(3) of Directive 2001/83/EC), the results of the assessment currently are not considered as a ground for refusal. The ERA is excluded from the B/R balance and as per the ERA guideline the environmental impact of a medicine “*should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered. In any event this impact should not constitute a criterion for refusal of a marketing authorisation”.*

The absence of a provision to enforce this requirement, pre-authorisation and post-authorisation, hampers the (timely) completion of ERA dossiers and stakeholder access to this information.

***Legislative solutions***

The proposed solution is to introduce provisions to enforce the submission of a complete and satisfactory ERA dossier pre-authorisation, and if requested also post-authorisation. This could be achieved in two different ways:

1. To introduce a stand-alone ground for refusal when risks to the environment and/or public health via the environment (including antimicrobial resistance) have not been sufficiently and satisfactorily addressed by the Applicant. This would be in line with the approach taken in the context of veterinary medicinal products, where in the new

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<sup>5</sup> [Recommendation on the use of Environmental Footprint methods \(europa.eu\)](https://ec.europa.eu/health/medicines/quality/era/era_guideline_en)



legislation such a standalone ground for refusal was added (Article 37(2)(i) Regulation (EU) 2019/6).

**Advantage:** This would draw the importance on the complete and timely assessment of the environmental aspects and strengthen the motivation of the Applicant to fulfil those requirements. This will also avoid mixing concepts of the B/R balance, where it will be difficult to weigh risks and benefits to the patients with environmental aspects and public health issues via the environment.

**Drawbacks:** A refusal of a marketing authorisation would need to be carefully considered (i.e. refusal in such cases should be deemed only a last resort measure, should major objections regarding ERA not have been sufficiently solved) as it might be perceived as disproportionate if solely based on an unsatisfactory ERA or risks to the environment, particularly when there is an unmet medical need. Measures taken should not negatively affect access to medicines when there is an unmet medical need. Such approach would also diverge from the European Parliament's recommendations *to strengthen the environmental risk assessment requirements and conditions for the approval and use of medicines, provided that marketing authorisations are not delayed or refused solely on the grounds of adverse environmental impacts* (see point 154 of [ENVI Report](#) on a pharmaceutical strategy for Europe (2021/2013(INI)).

2. To include risks to the environment as part of the B/R balance. This could be done by removing 'first indent' from the text in Article 1(28a) Directive 2001/83/EC.

**Advantages:** This measure would appear more proportionate as the risks to the environment and to patients would be balanced against benefits of the medicinal product and unmet medical need. As the B/R balance is understood as a process in which all positive and negative impacts are weighed against each other, it is unlikely that negative environmental effects, as a sole concern, would overrule clear clinical advantages. If an environmental risk is identified after the marketing authorisation, a review of a B/R-balance should be performed via existing procedures and documents.

**Drawback:** Including ERA within the B/R balance would lead to the difficult comparison of benefits and risks falling to different interests (patients versus public health and environment), and it will be difficult to ensure a consistency in the assessment and a fair treatment of all Applicants. In addition, this may have an impact on all existing procedures and documents which contribute to the review of the B/R balance (e.g. Risk Management Plan, Renewal procedures, Periodic Safety Update Reports) as well as on the remit of the PRAC who is involved in the review of the B/R balance.

Additionally, other legal provisions may be introduced in combination with one of the options above. This would enable regulators to take consistent action, when considered needed, pre- and post-authorisation, when the Applicant/MAH fails to meet the requirements for a timely submission of a complete ERA as well as for appropriately mitigating risks to public health and the environment.:

- Introducing a new provision to impose risk mitigation measures or ERA studies as conditions to the marketing authorisation or Specific Obligations (amendment of Article 21a, 22 and 22a of Directive 2001/83/EC and Article 5 of Commission Regulation

507/2006). When it can be agreed that the risks to the environment have been sufficiently addressed at time of authorisation but would require generation of further data to monitor risks to the environment and/or to public health in the post-authorisation setting, such post-authorisation studies should be imposed to the MAH as conditions to the marketing authorisation. Failure to complete those conditions could lead to an action on the marketing authorisation. It would be a matter of scientific assessment to weight the importance of the data to generate and decide whether to enforce the completion of these studies as conditions to the MA or to request it as a commitment. Currently, the instrument of Annex II conditions is not applied for environmental aspects, but mainly to further study efficacy or safety in the long term.

For Conditional Marketing Authorisations or MA under exceptional circumstances, the Applicant may have not been in a position to fulfil the ERA requirements pre-authorisation, therefore the possibility to impose ERA studies as Specific Obligations would need to be added as legal provision. The possibility to impose Annex II conditions or Specific Obligations on environmental studies would need to be carefully considered so that it does not appear as a circumvention of the ERA requirements (especially in case of a potential risk), which will affect also other stakeholders like water managers. It should take into account under which conditions a delay in availability of ERA data after authorisation may be acceptable.

- Introducing a new provision to initiate a referral when risks to the environment and/or public health have not been mitigated in a sufficient and satisfactory manner or when new information arises, similarly to Art. 82 of the vet legislation (Regulation (EU) 2019/6)
- Introducing an obligation for MAHs to comply with ERA requirements at time of marketing authorisation and during the lifecycle of the product (e.g. fulfilment of conditions to the MA) and to inform Competent Authorities of any new information that could impact public health and/or the environment (so that penalties could be considered if these obligations are not fulfilled) (Article 118a of Directive 2001/83/EC, Annex II of Regulation 726/2004 to be amended).

### ***Non-legislative solutions***

- In addition to the legislative changes, it would need to be clarified in the EMA guideline on ERA that failure to provide a satisfactory ERA could lead to the refusal of a marketing authorisation either under the existing Article 26.2 of Directive 2001/83/EC: “Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c,” (for centralised procedure – under existing Article 12(1) of Regulation 726/2004: “Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC”), or under the new ground for refusal (either a new standalone ground for refusal or under Article 26(1) of Directive 2001/83/EC (and Article 12(1) Regulation (EC) 726/2004), if the risks to the environment and/or to public health are added to the B/R balance.
- Applicants could request scientific advice on completeness of the ERA package (possible fee reductions for scientific advice could be considered when ERA studies are required).

#### **1.1.1.3 Reinforcing risk mitigation measures**

### ***Problem statement***

As stated in section 1.1.2.2, impact on the environment is explicitly excluded from the B/R balance in accordance with art. 1(28a) of Directive 2001/83/EC.

Art. 8.3 of Directive 2001/83/EC requires the Applicant to provide the following for all marketing authorisation applications:

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.”

Despite these requirements, in practice, in the vast majority of applications reviewed, these measures are limited to the same standard statements in the Product Information, regardless of the outcome of the ERA. These statements are not mandatory and of limited significance for the environment protection and provide generic guidance on waste:

- Summary of Product Characteristics/outer labelling: <No special requirements <for disposal>.> or <Any unused medicinal product or waste material should be disposed of in accordance with local requirements.>
- Package Leaflet: <Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.>
- according to art. 127b, a reference to any appropriate collection system in place for medicinal products that are unused or have expired, should be included in the Blue Box (i.e. at national level) on the outer packaging.

Although some emissions of pharmaceuticals occur due to inappropriate handling of waste / unused pharmaceuticals, the majority of emissions originate from the excretion of medicinal products taken by patients<sup>6</sup>. No risk mitigation measures are currently applied that reduce this emission via the patient to the environment with the exception of special medicinal products such as radiopharmaceuticals (radioactive medication) where local requirements on collection schemes of patient excretions after treatment are in place.

Besides this, currently there are no requirements for post-approval monitoring emissions of pharmaceuticals into the environment, e.g., by reporting consumption data in the Member States or monitoring of environmental concentrations of relevant substances.

In conclusion, if there is a risk identified for the environment, there are currently no legally binding requirements for risk mitigation measures in the value chain.

### ***Legislative solutions***

Expand the scope of risk mitigation measures when a potential or identified risk is associated to the therapeutic use of a medicinal product and make them mandatory. This should include more than labelling of the risk. Risk mitigation measures should be designed to actually reduce environmental impacts. The obligation to provide effective (effectiveness to be demonstrated) risk mitigation measures by the Company should be included in the pharmaceutical legislation.

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<sup>6</sup> According to estimates by pharmaceutical companies, the main sources of human medicinal products in surface waters are patient excretions (88 %), improper disposal down sinks or toilets (10 %) and manufacturing processes (2 %). ...” <https://www.umweltbundesamt.de/bg-micropoll>

Risk mitigation could be achieved – amongst others – with the possibility for a medicinal product to:

- restrict its use EU-wide to prescription-only (Article 71 of Directive 2001/83/EC should be amended to include environmental risk as condition for medical prescription),
- limit its advertising,
- establish environmental monitoring schemes, including setting environmental threshold limits,
- establish agreements for information exchange with other regulatory bodies,
- include a mandatory report on environmental impact (or lack of data) in the summary of product characteristics, which needs adaption of Art. 11 for “5.4 environmental properties”,
- review the ERA dossier when the target population is increased (extensions of indication, line extension), or when monitoring data or scientific literature provide new information (see Section 1.1.2.5).

Other realistic and pragmatic risk mitigation measures could be designed along the same principles as previously done for veterinary pharmaceuticals **Error! Bookmark not defined.** It is important that the legislation strengthen these measures making them legally binding, irrespective of the inclusion of the ERA in the B/R balance (Section 1.1.2.2).

Part of risk mitigation could also be to enforce the obligation to monitor the effectiveness of the risk mitigation measures proposed by the Company, in line with the other legal provisions (i.e. ground for refusal, triggering of a referral), monitoring data and information on use of substances with an identified risk and/or hazard to the environment could be imposed as part of conditions to the Marketing Authorisation (Annex II conditions) and/or Specific Obligations instead of being requested as recommendations.

Mandatory risk mitigation measures should go hand in hand with mandatory completeness and timelines of dossiers (see Section 1.1.2.2), otherwise this could be a disincentive to submit a completed ERA.

Risk mitigation measures should consider that there may be more products with the same active substance. Thus, risk mitigation measures should be harmonized between similar products, which may have to be enforced via a referral procedure.

### ***Solutions on a guideline level***

A guideline or reflection paper needs to be developed on which risk mitigation measures are to be applied, like the reflection paper for risk mitigation measures for veterinary medicinal products **Error! Bookmark not defined.**

A guideline needs to be developed on how to weigh environmental impact (including other sustainability aspects) in order to compare different substances and/or products, e.g., to be used for sustainable procurement. This would be in line with the recently published EU Commissions ‘Recommendation on the use of Environmental Footprint Methods’<sup>5</sup>. Regardless of whether environmental impact is part of the B/R balance, such a comparison system should include safety and efficacy for the patient and be aligned with the B/R balance as currently described in e.g., the day 80 assessment report guidance.

#### **1.1.1.4 Linking Pharmaceutical and environmental legislation**

### ***Problem statement***

Currently, there is no link between the pharmaceutical legislation and environmental legislation (e.g. Directive 2000/60/EC). This hampers the risk assessment and possible risk mitigation measures and does not fit with the EU's Zero pollution ambition. Currently, when an environmental risk, or a hazard, is identified within the marketing authorisation procedure, this outcome is not 'flagged', nor communicated to competent authorities for environmental management. Even when no risk is identified, environmental data from the pharmaceutical authorisation process could be relevant for policy under different environmental legislative frameworks like the Water Framework Directive (2000/60/EC), the Groundwater Directive (2006/118/EC), the Urban Wastewater Treatment Directive (91/271/EEC, amended by 98/15/EC), the Drinking Water Directive (2020/2184) or the Industrial Emissions Directive (2010/75/EU) for using it for the derivation of environmental quality standards or emission limit values.

Vice versa, when a signal is identified based on monitoring data this is not communicated back to the regulatory authorities and the marketing authorization holder (MAH) and relevant risk mitigation measures are not taken by the MAH as pharmaceutical legislation lacks any regulatory actions or obligations to do so.

### ***Solutions***

The pharmaceutical legislation should be coupled to other environmental legislations to facilitate exchange of monitoring data and risk assessment results. Environmental data received in context of the pharmaceutical legislation should not be limited for use in other legislative frameworks by confidential restrictions. Study results and their assessment, including the Predicted No Effect Concentration (PNEC) and risk quotient, may be shared as they cannot be used by others in their marketing authorisation dossier<sup>7</sup>. Thus, part of this issue can be solved by making ERA results (including study endpoints) publicly available (e.g., via EPARs) and easily retrievable (see Section 1.1.2.6).

A legal provision should be proposed to list active substances in a central database available for competent authorities for environmental management, and other stakeholders such as the health care sector and the public. Regular revisions of the data are necessary. The monograph system (see Section 1.1.2.6) could be used to transparently report the relevant data.

Legal provisions added should also foresee that national authorities responsible for environmental management may provide feedback on environmental issues due to the use of pharmaceutical products, e.g., based on monitoring data, to NCAs and to EMA. This provision should ensure that environmental risks identified (e.g., via environmental monitoring) should be reported to EMA as part of the ecopharmacovigilance framework. For these substances, a mandatory process of reviewing the ERA should be applied, including application of mandatory risk mitigation measures if a risk is identified based on environmental monitoring data, e.g., within other legislative frameworks.

Furthermore, it is suggested to include a link to the new Regulation (and Regulation 2019/6 on vet meds) into article 7a of the Water Framework Directive during the next revision.

#### **1.1.1.5 Re-evaluation of the ERA during the life-cycle of a medicinal product**

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<sup>7</sup> Andrea M. Keessen, Annelies Freriks, Marleen van Rijswick, 'The Clash of the Titans: The Relation between the European Water and Medicines Legislation', CMLRev (5) 2010, pp. 1429-1454  
[Common Market Law Review \(kluwerlawonline.com\)](https://www.kluwerlawonline.com)

### ***Problem statement***

The ERA conducted at authorization is not re-evaluated, while new environmental information may become available from monitoring data or scientific literature. The result is that risk mitigation measures in the SmPC or PL may be obsolete, and the information exchange within the value chain is not effective.

### ***Solutions***

The ERA should be reviewed when triggered by signals from (post)authorization procedures, scientific ecotoxicology literature or environmental monitoring, or for first-in-class active substances. This re-evaluation should be more often for products with an identified risk. Signals from (post)authorization procedures could include intrinsic hazardous properties, a risk quotient just below the trigger value, and increased use due to increased target population, for example when patents expire.

The industry (EFPIA, AESGP, EGA) have proposed in their eco-pharmaco-stewardship initiative - pillar 3 Extended Environmental Risk Assessment to come up with a system to share data amongst applicants and marketing authorization holders (see below). This is then followed by a regular re-evaluation<sup>8</sup>. The industry proposal is endorsed. However, re-evaluation should not be voluntary, and still ensure that important new medicines continue to be routinely available to patients.

The legislation should be amended to include a provision for a regular re-evaluation of the ERA. The re-evaluation dossier should be the responsibility of the MAH (originator) before expiry of patent (as suggested by the industry proposal above). The MAH should be responsible for any additional follow-up studies agreed with the regulatory agencies, in order to investigate, refine and resolve risks identified in the original ERA, to evaluate newly published data, and to evaluate the ERA results based on new data on total use of the relevant substances and their environmental concentrations and effects.

After expiry of patent(s) or another agreed time period, all MAHs (including generics/Hybrids/biosimilars) should contribute to the re-evaluation of the ERA which should take place on a risk-based interval defined by a regulatory body (e.g. ERA working party), based on the results of the most recent ERA. This regulatory body should define the interval and data needed to be submitted by the MAHs for re-evaluation, within the frame of ecopharmacovigilance. The monograph system (see Section 1.1.2.6) could be used to accommodate this review.

Medicinal products containing legacy substances (i.e., products authorised prior to Dec 2006) are not in the scope of the proposed ERA re-evaluation approach, but are discussed in section 1.1.2.6. A prioritisation approach, as prepared by the IMI PREMIER project (see appendix) should be used to obtain ERA dossiers for legacy substances. Depending on the results of these ERA dossiers, also for these active substances a re-evaluation approach would be the next step.

### ***Legislative changes***

- Introducing a new provision to initiate a referral when risks to the environment and/or public health have not been mitigated in a sufficient manner or when new information

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<sup>8</sup> <https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/>

arises, similarly to Art. 82 Regulation (EU) 2019/6 regarding veterinary medicinal products

- Introducing an obligation for MAHs to comply with ERA requirements also during the lifecycle of the product (e.g. fulfilment of conditions to the MA) and to inform Competent Authorities of any new information that could impact public health and/or the environment become available (so that penalties could be considered if these obligations are not fulfilled) (Article 118a of Directive 2001/83/EC, Annex II of Regulation 726/2004 to be amended).

#### **1.1.1.6 Data transparency, data sharing, monograph system, database, and catching-up procedures**

##### ***Problem statement on availability and transparency of environmental data***

Availability of (environmental) data on chemicals is part of the EU Commission's Chemicals strategy, including a request for harmonisation of data ('one substance, one assessment'). Besides this, it is important to transparently provide relevant environmental data to stakeholders like water managers, the health care sector, the research community, as well as the public. They need such environmental data on active substances to e.g., evaluate monitoring data and to establish mitigation measures.

Currently some environmental endpoints are made available in the (E)PARs of the authorized products, but this is not always the case or not all relevant (and non-confidential) information is disclosed. Depending on the procedure type, these (E)PARs are published by EMA or the Reference Member State.

Many ERA data were provided after the first marketing authorization because of incomplete ERAs or increasing environmental concentrations due to new indications. Usually, environmental sections in (E)PARs are not updated with the results of these variations.

There is no centralised inventory of active substances for which ERA data are available. As the (E)PARs are product based, environmental information on active substances may be hard to find when these data are published product based in large reports and not directly linked to the active substances. Moreover, many of these refer to unspecified other products with the same ingredient for the ERA and do not contain the data themselves.

Increased public access to environmental information should be in line with the objective of Directive 2003/4/EC of the European Parliament and of the Council of 28 January 2003 on public access to environmental information and repealing Council Directive 90/313/EEC. Furthermore, it fulfils the right of access to environmental information according to Art. 2(3)(b) Aarhus Convention as summaries of the ERA may not be classified as commercially/industrial confidential information. Summaries cannot be used by other MAHs for their marketing application, because the data are in the ownership of the former applicant. Publicly accessible ERA data would also fit with the aims of the "Chemicals Strategy for Sustainability" that "data should be easily findable, interoperable, secure, shared and reused by default". Data transparency is one of the main goals of the 'One substance, one assessment' principle of the European Commission.

##### ***Problem statement on legacy products without ERA***

Human medicinal products put on the market before 2006, when the EMA guideline on ERA of human medicines came into force, often lack an adequate ERA. Until now, environmental

fate and effect data are available only for less than a third of the active substances of potential environmental concern (in reference to their chemical nature). Consequently, there are many medicinal products on the market with a high usage whose environmental impact has never been investigated. The need to implement a review program for 'legacy' products into the EU legislation was also recognised by the EU Strategic approach to pharmaceuticals in the environment (COM(2019) 128 final).

Furthermore, ERAs for generic applications are formally requested (see Art. 10 Directive 2001/83/EC), but in the current EMA guideline on ERA, these are exempted from a further ERA if the applicant shows there are no significant changes in use. This also applies to generics of products authorised before 2006, for which no ERA is available at all. However, if an increase in environmental exposure is expected, providing a complete ERA dossier could be a big effort for small to medium enterprises. This results in a lack of level playing field, as these costs have not been made by other companies that already marketed similar products. All in all, the current system neither supports the provision of urgently needed data, nor ensures an equal treatment of the applicants.

### ***Problem statement on product based assessments and lack of data-sharing***

In the current legislation each applicant has to provide its own environmental risk assessment with own study reports. With regard to generics, Article 10 of Directive 2001/83/EC makes reference to the derogation of the requirement for non-clinical and clinical data laid down in Article 8(3) (i), but not Article 8(3) (ca), which lays down the requirement for ERA. Consequently, there may be different dossiers in terms of ERA for similar products with the same active substance. For each generic application where an increase in consumption of the active substance is indicated (see also the problem statement above), an ERA must be submitted. This could result in diverging conclusions between similar products. Furthermore, multiple testing of the same active substance leads to repeated costs and resources for applicants and assessors. Especially for vertebrate (fish) studies this is not in line with the Directive 2010/63/EU on the protection of animals used for scientific purposes (3Rs). Thus, although data sharing is recommended by regulators, it is rather the exception than the rule and a system for data sharing has not been established yet.

### ***Legislative solutions***

**The solutions for the three issues identified above all lie along the same line:**

- **A monograph system should be established, with a central repository of quality-assessed ecotoxicity data per substance. Provisions on data sharing should support applicants to provide, share, and use data for their product-based ERA, which will only differ in the calculation of expected exposure based on the use profile of the product.**
- **The study results should be available to other stakeholders in the form of endpoints/study summaries (study reports will remain confidential and are owned by the individual companies), supported by a database.**
- **As development of a monograph system will take some time, in the meantime a public database with ecotoxicity data for relevant substances should be established. This database should contain study results (endpoints), as currently provided within the (E)PARs. Study reports will remain confidential and data are formally owned by the individual companies.**
- **Legal provisions should enable data sharing between companies. For vertebrate (fish) studies specifically, complying with the 3R principles, mandatory data sharing should be in place.**



- **Provisions for a catching-up procedure for legacy products (products authorised before 2006 and products authorised after 2006 which refer to reference products without an ERA) are needed to make sure the subsequent monograph system contains information for all relevant substances. The monograph system can further be used for re-evaluation of ERAs.**

‘Environmental monographs’ on active pharmaceutical substances and environmentally relevant excipients should be established, comparable to monograph systems currently used within the REACH, biocides and plant protection products frameworks. These monographs would contain a comprehensive set of valid physiochemical data, fate, and effect data, which have been quality assessed by regulatory assessors. Thus, the monograph system will prevent different outcomes of ERAs for similar products containing the same active substance, as it provides for centralised substance-based assessments driven by a validated set of substance-based tests. The shared use of ERA data has to be based on clear rules on data confidentiality and financial arrangements. Data sharing options as provided under REACH might also be useful in order to implement them within the pharmaceutical sector.

The feasibility of such a monograph system for veterinary medicinal products has been evaluated recently<sup>9</sup>. The feasibility study showed that a monograph system is justified, proportionate and affordable. Furthermore, high environmental benefit could be expected as

- Test data for environmental impact assessments will be optimized and consolidated;
- Test duplication is avoided, which will contribute to the 3Rs (reduce studies on animals);
- Conclusions on risk will be harmonized, as the same study outcomes are used for different products;
- There will be better access to ERA data for environmental authorities, experts and the public;
- This leads to more transparency and improved data sharing.

So, issues identified under the problem statement are all covered by the development of a monograph system for human pharmaceuticals. The implementation of such a system should be a legally binding process in the new regulation.

A centralised work-sharing procedure could be set up to assess the quality of the ecotoxicity tests in the monograph system. This system could be similar to what is currently done for the ASMF (Active Substance Master File) and based on best practices from e.g., the biocides or plant protection products frameworks.

Once established, all applications for marketing authorisation of a medicinal product should use the agreed information from the ‘monograph’ of the respective substances to perform the ERA of their medicinal product based on its specific use and subsequent exposure profile. This way, the Monographs will provide for a substance-based assessment with product-based exposure assessment, which is an important tool towards a harmonized registration and risk assessment for active substances, as targeted in the Commissions ‘One Substance, One Assessment’ approach. This will also facilitate exchange across different legal frameworks, when dealing with the same active substance.

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<sup>9</sup> <https://op.europa.eu/en/publication-detail/-/publication/03055c4d-42a6-11ec-89db-01aa75ed71a1/language-en/format-PDF/source-243449059>

As the monograph system should contain data for all relevant substances, a catching-up procedure for active substances in legacy products is therefore needed. Such a procedure needs to be detailed in terms of responsibility and prioritization of substances. In any case, a catching-up procedure should start with substances that have an identified risk in other legislative frameworks (e.g., WFD) or other prioritisation exercises.

It is proposed to include the provision that an implementing act needs to be written on the monograph system, data sharing, and a catching-up procedure. For example: “[EU body], in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of environmental fate and effects data regarding medicinal products marketed in the Union intended to allow all competent authorities to share the information at the same time. This should include a procedure for products authorised before 2006 and products with active substances for which no environmental risk assessment has been performed because they refer to reference products without an ERA.” Further instructions on which data should be implemented in the monograph system should be addressed in Annex I: *Study data relevant for the Environmental Risk Assessment (including data on toxicology if required for the risk assessment) should be part of the ‘environmental monograph’.*

If a new article on development of a monograph system is included (e. g. with empowerment for the EC to adopt delegating [implementing] acts) in the new Regulation, in the mean time a provision should be added to include mandatory data sharing of vertebrate (fish) study results. Applicants would still need to provide their own ERA with their specific exposure scenarios, including fate tests and tests on invertebrate species.

Additionally, there should be a provision for submission of post authorisation ERA studies to ensure that the data in (E)PARs and/or the database is updated with ERA information.

#### ***Non-legislative aspects: Proposals for setup and design of a database***

The database and subsequent monograph system should be developed under supervision of a European Union body and maintenance should also be the responsibility of this body. To start with, the database should be fed with data from all centralised and national procedures, including new data from post-authorisation commitments, variation applications, catching-up procedures, and potentially also public literature sources. The quality of these data (regulatory accepted during authorisation, reliability assessed, or not assessed) should always be clear. Member states should be obliged to provide the data received in decentralised or national procedures. Data from the catching up procedure of active substances in legacy products can be included. Any database should be made compatible with similar databases and tools, especially managed by ECHA to be in line with the one substance one assessment approach of the Commission.

Awaiting the setup of a monograph system, which will take considerable time, an amendment to the current Regulation should provide for a central database of all environmental data for each substance and the outcome of the ERA and the hazard assessment for each product, such as risk limits (PNECs), classifications (PBT or vPvB) and risk quotients, including results (endpoints or summaries) from the underlying studies. As stated above, summaries cannot be used by other MAHs and thus there should be no confidentiality issues. A starting point for such a system could be DAS (Database and Assessment System) currently developed within the IMI PREMIER project (see section 1.3).

While awaiting the setup of the monograph system, the database will already make it easier for applicants to share their data, as it will become more clear which data are already there and

which MAH holds ownership. Thus, the database can help to solve the issue of unnecessary repeated testing. The shared use of ERA data in the data base by various applicants has to be based on clear rules on data confidentiality and financial arrangements. Data sharing options as provided under REACH might also be useful for the pharmaceutical sector.

The industry (EFPIA, AESGP, EGA) have proposed in their eco-pharmaco-stewardship initiative - pillar 3 Extended Environmental Risk Assessment<sup>8</sup> to come up with a system to share data amongst applicants and marketing authorization holders: Originator companies will share ERA data for free with generic companies once the data protection period has ended, and generic companies will share the costs for ERAs for substances not yet assessed (authorized before 2006). This is then followed by a regular re-evaluation: more often for substances with a risk, less often for substances with no predicted risk. This proposal could be endorsed, but should not be voluntary.

The functionality of the database should serve various purposes, which may be identified based on so-called ‘user stories’, based on questions like ‘is it to identify stakeholders that have conducted ERAs for certain active substances in order to procure a Letter of Access?’, ‘is it only for regulatory/industrial purposes or to provide a basis for environmental policies?’, ‘is it for eco-pharmacovigilance and to inform environmental quality bodies?’, ‘should it include information from relevant academic studies, or provide information to academic researchers?’.

Currently, a database that could serve as a good model concept for developing proposed solutions is under development by the PREMIER consortium (IMI-premier – Prioritisation and Risk Evaluation of Medicines in the EnviRonment), consisting of several EFPIA companies, universities, research institutions, RIVM and EMA (see section 1.3). After the PREMIER project has ended, the database should be sustained on a structural basis. The PREMIER consortium is in the early stages of discussing with EMA how this could be achieved and who should be in the management group for this database and be responsible for the quality. The EFPIA companies have offered a model to finance (partly) the costs for maintaining the database, but the consortium is open to other options.

An option for the database could be to use emerging data platforms, like DG ENV’s Common Open Platform on Chemical Safety Data (COPCSD), which could be considered as a key technical enabler of the ‘One substance, One assessment’ approach where authorities have access to a common dataset to fulfil their mandate under applicable legislation.

Similar situations can be found in other legislations:

- REACH: industrial chemicals were registered under IUCLID (International Uniform Chemical Information Database), it is available via the ECHA website. ECHA makes available this information as REACH registered substance factsheets, which contain the full set of non-confidential information from related registration dossiers for a substance. However, data were not quality checked and ‘published as provided’. IUCLID is a software application for recording, storing, maintaining and exchanging environmental data of chemical substances and mixtures. The backbone of IUCLID are the OHTs (OECD Harmonised Templates).
- Veterinary pharmaceuticals: the need for a general review of rules for environmental risk assessment was recognized in the new regulation on veterinary medicinal products (2019/6). Conclusions of the feasibility study carried out under Art. 156 of Regulation (EU) 2019/6 on veterinary medicinal products can be taken into account when considering a monograph system for human medicines.

- Biocides: Database on biocidal active substances is available via ECHA websites (IUCLID database). The data are active substance/product-type centric, allowing for searching and displaying information per active substance/product-type combination. The results table presents information on an active substance, such as approval start and end date, evaluating competent authority and approval or assessment status. The substance name is a link to the substance information page (Infocard) which summarises information on a substance from all regulatory contexts managed by ECHA. The data on active substances is collected from the Register for Biocidal Products (R4BP 3). It covers information on active substances for which an application for approval for a specific biocidal product-type has been submitted under the BPR or Biocidal Products Directive (Directive 98/8/EC).
- Plant protection products: For those, a pesticide properties database has been established, available at <http://sitem.herts.ac.uk/aeru/ppdb/en/index.htm>. The database has been developed by the Agriculture & Environment Research Unit (AERU) at the University of Hertfordshire for a variety of end users to support risk assessments and risk management, so basically with the same goal as proposed here for human pharmaceuticals.

### **1.1.1.7 Quality and harmonization of assessments and increased collaboration**

#### ***Problem statement***

The quality of assessments differs between member states. Not all MS have ERA expertise, because the ERA is not part of the B/R balance it gets little priority. As a result, there is a lack of harmonization of assessments. The environmental risk assessment and its required studies differ significantly from toxicological studies in the preclinical assessment. Specific expert knowledge is required on eco-toxicological effects and exposure scenarios. Only in a limited number of Member States specialised environmental experts perform the ERA assessment. Thus, the environmental expertise of the ERA assessors in the different member states varies considerably. This leads to different assessments and sometimes inconsistent treatment of applicants.

Training topics, e. g. on PBT assessment or tailored risk assessment, were included in the agenda of the informal meetings of ERA assessors, organised voluntarily by different MS every year. However, as there is no financial support for these informal meetings, the authorities must be prepared to cover the costs of participation. In 2017 there was a training with cost reimbursement for the participants by the EU NTC of EMA (one participant per MS; travelling costs and accommodation for duration of the training). For the organisers, the training sessions require a considerable amount of time and resources, especially in terms of manpower, making it not feasible every year.

At EMA no ERA working group for human pharmaceuticals is installed. The responsible working party for ERA issues is the Safety Working Party, which is mainly focussed on patient safety issues. An ERA drafting group was installed to review and prepare the guideline for revision. There is no group available discussing ERA issues in on-going procedures or being available to reflect on e. g. new approaches in risk assessment.

#### ***Legislative solutions***

There is no real solution on legislative level, although it is argued that when the ERA and its consequences becomes a mandatory item, member states will invest more in environmental expertise.

### ***Solutions on guideline level***

There needs to be more formal training e.g., as a European regulatory initiative (e.g. EU Network Training Centre (EUNCT) program at EMA).

Harmonisation of the ERA assessments might be further reached by generally approachable database (see Seciton 1.1.2.6).

The AdHoc WG under the Pharmaceutical committee has proposed other non-legislative solutions like

- Regular training opportunities in presence and online
- Twinning between experienced and less experienced Member States who may discuss their difficulties with actual dossiers
- Online Platform
- Designation of contact persons for ERA issues

However, care should be taken that these are not voluntary solutions, as then these would still depend on volunteer Member States and not result in the required harmonization and increased expertise in all Member States.

## **1.2 Strengthening the conditions of use for medicines**

### **1.2.1 Current situation**

As regards the environmental challenges due to the use of medicines, Directive 2001/83/EC sets a framework to address these issues in the authorisation application as the following information needs to be included in that application as provided by Article 8 point (g): “*Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.*”

As regards the centrally authorised medicinal products, Regulation (EU No 726/2004 also sets a corresponding requirement by making reference in Article 6 to the provisions of Directive 2001/83/EC: 1. Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. In addition, Article 13(3) second paragraph of that Regulation sets the provision that sets the rules for transparency of information in relation to the conditions of use as it says “*The European Public Assessment Report (EPAR) shall include a summary written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.*”

Moreover, Article 127b of Directive 2001/83/EC also provides that the EU Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

The EU Strategic approach to pharmaceuticals in the environment has set an action currently under ongoing implementation under the WG on pharmaceuticals in the environment mandate. For that the subgroup on environment of that WG assesses the implementation of collection schemes for unused pharmaceuticals in the MSs including best practices. This group will provide recommendations how their availability and functioning could be improved, how to increase public awareness of the importance of using them, and how extended producer responsibility could play a role in reducing inappropriate disposal.

### ***General problem statement***

The size of the package is closely related to the dosage and composition. For some medicinal products, it is impossible to reduce the packaging. Environmental impacts due to the use of pharmaceuticals may concern more aspects than emissions after administration (via urine and faeces). This also concerns spillage of medicines: too many doses are distributed to the patient, with vast amounts of left-over medication as a result. Due to short shelf-lives, many pharmaceuticals may be discarded before they are used, even if their quality is still compliant for the intended use. Environmental consequences are that more products need to be manufactured and more waste is being produced, which is both unnecessary. From a general sustainability point of view, this concerns not only the active substances and relevant excipients, but also other materials (e.g., packaging, devices for administration). For the waste stage, appropriate collection systems are not always in place. Besides this, conditions of use could be strengthened for active substances or excipients with a risk, like provisions to not allow these medicinal products to be dispensed other than via prescription (e.g., no over the counter sales) or other risk mitigation measures (linked with above).

### **1.2.2 Issues and solutions**

Lack of appropriate use or spillage of medicines may be impacted by

- Pack sizes
- Shelf-life
- Other aspects

Besides this, reducing environmental emissions may need changes regarding

- Disposal of unused medicines / Waste collection systems
- Risk mitigation, including over the counter sales

These issues are discussed below in more detail with their solutions.

#### **1.2.2.1 Pack sizes**

##### ***Problem statement***

The choice of pack sizes in terms of number of unit dosages or total amount in the container (e.g. cream, paste) is defined by the applicants/MAHs. There is no provision in the EU legislation to take into account environmental aspects with regards to the choice of pack size. In case of variations, justification for the new pack size(s) is to be provided if outside the range of currently approved pack sizes. This usually entails showing that the new size(s) is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics. If within the approved pack size, a simple “do and tell” IA variation may be submitted. However, conditions for supply (i.e., hospital use or pharmacy sales, with or without prescription) may impact the evaluation of the proposed pack size: these aspects are managed at national level, outside the dossier and MAA.

##### ***Legislative solutions***

Environmental issues should be considered as part of the decision on proper pack sizes, mainly with regard to non-prescription products. This should take into account that the size of the package is closely related to the dosage and composition. For some medicinal products, it is impossible to reduce the packaging. A provision should be added to the legislation that products with an identified risk to the environment or to public health (e.g. high risk of antimicrobial resistance) should meet the unit-dose labelling requirements in order to be dispensed to the

exact quantity prescribed. This would reduce waste and emissions into the environment as well as reducing misuse.

Another legislative solution would be to oblige marketing authorisation holder to market only packages containing the exact quantity according to the amount prescribed. This is a more stringent measure which could contribute to reduce waste and inappropriate disposal of medicinal products. Besides this, pharmacists could be obliged to dispense only the exact quantity of medicine prescribed (as is done in the UK).

Change in variation classification guideline (for type IA variations), is to be considered.

### ***Non-legislative solutions***

Further address the issues via sharing of best practices, possible guidance documents, whenever needed and appropriate also in the implementation of the EU strategic approach to pharmaceuticals in the environment.

#### **1.2.2.2 Shelf-life**

##### ***Problem statement***

The shelf-life/expiry date of medicinal products is defined based on the stability data provided by the applicants in the dossier supporting the MAA. Relevance of shelf-life aspects are becoming more important as MAHs may be requested to have safety stocks by the EU in future.

A shelf-life extension will only be approved if the MAH submits a variation requesting it. There is no provision in the EU legislation to force or to incentivise MAHs to continue to evaluate a product's stability, nor to extending the shelf-life, beyond that approved at the time of the first MA. Therefore, it is possible that the approved shelf-life of several medicinal products is shorter than that would otherwise be observed, if additional stability studies were to be conducted and related data to be provided to competent authorities. If the MAHs opt not to submit a variation to extend shelf-life, regulators are in no position to request a change. This eventually results in the disposal in the environment of unused medicinal products which would otherwise still be of acceptable quality. Similar considerations apply to the establishment of in-use shelf lives of multidose products.

According to the current variation classification guideline, a MAH can request a shelf-life reduction via a type IAIN variation without any justification, provided that the change is not due to unexpected events during manufacture or due to stability concerns. This reduction is often requested for "commercial" reasons only and Competent Authorities cannot refuse approval of such variations as there is no legal basis for not approving them. Indeed, if that condition ("The change should not be the result of unexpected events arising during manufacture or because of stability concerns") is met, being a type IA variation, the change may have been already implemented at the time of submission and no further evaluation of the consequences of such a change can be performed.

##### ***Legislative solution on a legislative level***

A legislative action on this topic is needed to encourage or mandate MAHs to pursue further stability studies and to apply for shelf-life extensions after marketing approval, wherever possible.

##### ***Non-legislative solution***

Change in the variation classification guideline, excluding the reported condition or proposing a type IB variation for shelf-life reduction (as already foreseen in case of extension of the shelf-life of the finished product), is needed.

### **1.2.2.3 Other aspects**

#### **Redistribution**

Many patients do not use all medication that they get dispensed. This leads to unnecessary spending of financial resources, unnecessary production and distribution, and unnecessary medical waste. Re-dispensing unexpired medicines in a hospital context is only possible until 10 days after the first distribution, to prevent falsifications (Commission Delegated Regulation 2016/161 art. 13(1)(b) “the reverting of the status takes place not more than 10 days after the unique identifier was decommissioned”). Outside of hospitals, re-dispensing is not possible (art. 13(1)(e) recites “the medicinal product has not been supplied to the public.”). Under strict circumstances and the responsibility of the pharmacists, exceptions to this rule should be made (e.g., using loggers that show the temperature changes and provided that the package has not been opened). At least this could be considered for those medicinal products with high costs for national health systems.

#### **Responsible use, education, awareness raising**

Prudent use of pharmaceuticals is one possibility to reduce environmental exposure to pharmaceuticals. This can partly be achieved through so-called soft measures, e.g., training of clinicians, exchange of best practice and comprehensive communication of environmental properties and risks of medicinal products. However, this kind of measures can only be implemented effectively if environmental adverse effects are known and data are available and easily retrievable (see chapter data availability 1.1.2.6).

### **1.2.2.4 Disposal of unused medicines / Waste collection systems**

#### ***Problem statement***

Currently, the legislation is not clear enough concerning the responsibility of the manufacturer for making a sustainable choice of primary and secondary packaging materials and package volume that also allows for recycling. This could reduce transport volumes and facilitate recycling of materials. Disposal of medicines may be subjected to specific national laws for medical waste. According to art. 127b of the Directive 2001/83, a reference to any appropriate collection system in place for medicinal products that are unused or have expired, should be included in the Blue Box (i.e., at national level) on the outer packaging.

Nevertheless, many packaging materials, especially external secondary packaging, may be efficiently recycled after the use of medicine. Reference is made to the EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 94/62/EC of 20 December 1994 on packaging and packaging waste, as amended, article 8: “To facilitate collection, reuse and recovery including recycling, packaging shall indicate for the purposes of its identification and classification by the industry concerned the nature of the packaging material(s) used on the basis of Commission Decision 97/129/EC. Packaging shall bear the appropriate marking either on the packaging itself or on the label. It shall be clearly visible and easily legible. The marking shall be appropriately durable and lasting, including when the packaging is opened.”

Pharmaceutical waste collection systems are currently the responsibility of the individual Member States.



### ***Legislative solutions***

Include a clear requirement to include environmental aspects in the choice of packages/packaging materials for medicinal products. Both primary (immediate container/closure) and secondary packaging, are concerned. Reference should be made in the upcoming legislation to the Directive 94/62/EC on packaging and packaging waste as well as Directive 2008/98/EC on waste.

Moreover, some solution for disposal of unused or expired medicinal products containing active substances (besides the packaging) should be proposed: EU legislation, above national requirements, should be in place. This will help the MAHs to include in the dossier and product information clear instructions for disposal of medicinal products.

### ***Non-legislative solutions***

An alternative to the harmonisation of disposal at EU level could be to include detailed information on packaging materials in the content of the dossier and in the package leaflet together that would allow appropriate disposal/recycling of empty containers at Member State level. This could be reflected in relevant guidelines or in EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants For existing MA, notifications according art. 61(3) and 62 of Directive 2001/83 could be acceptable and encouraged: in this respect, it should be considered if these details could be under MAH responsibility, without the corresponding details in the dossier, in order to avoid an excess of information in the dossier, subject to future variations and consequent administrative burden for National Competent Authorities.

#### **1.2.2.5 Risk mitigation, including over the counter sales**

Conditions regarding use of pharmaceuticals should be stricter for pharmaceuticals for which the ERA, environmental monitoring or other signals identifies a risk to the environment. Risk mitigation measures should apply to such pharmaceuticals, e.g., no over the counter sales, no advertising, specific waste collection systems, etc.

### ***Solution***

Change in Directive 2001/83, art. 71 and TITLE VIII “ADVERTISING”.

Full application of art. 8.3 “The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(g) “reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment”, should be given.

#### **1.3 Results of research under the Innovative Medicines Initiative**

The aim of PREMIER (Prioritisation and Risk Evaluation of Medicines in the EnviRonment), a public/private partnership under the Innovative Medicines Initiative<sup>10</sup>, is to deliver a framework for assessing and characterising the environmental risks of active substances. This framework will be used to prioritise and screen older (‘legacy’) substances that have never been evaluated in an ERA. During the project period, ecotoxicity studies are performed to fill data gaps for 25 substances with the highest priority. Depending on the results of those studies, it should be clearer which other legacy substances or substance groups would need testing. The assessment tools developed in PREMIER may also be used to pick up potential environmental

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<sup>10</sup> <https://imi-premier.eu/>

risks of new active substances that are still under development, thereby contributing to greener drug design. PREMIER will make environmental data gathered within the context of the project visible and publicly accessible to all stakeholders. PREMIER consists of a consortium which includes the European Medicines Agency, universities, research institutes, small-to-medium enterprises, and EFPIA companies.

Currently, a database that would meet identified needs in the sections above is under development by the PREMIER consortium. After the PREMIER project has ended, the database could be sustained on a structural basis. The PREMIER consortium is in the early stages of discussing with EMA how this could be achieved and who should be in the management group for this database and be responsible for the quality. The EFPIA companies have offered a model to finance (partly) the costs for maintaining the database, but the consortium is open to other options.

In the DAS, endpoints will be available for all stakeholders with clear information on the reliability of this data and who has assessed that. EFPIA companies are working on a module to share ERAs and their study reports with generic companies and provide them letters of access. Depending on how the system is financed, this may even be free of charge. Regulatory assessors can then use the assessment module in the DAS, based on the ERA guideline, for a harmonized risk assessment using the available dataset.

PREMIER started in September 2020 and will run until September 2026. The results of the first year of the project are described in more detail in the Appendix to this Concept paper.

#### **1.4 Concluding remarks on section 1**

**Considering that pharmaceuticals should be available for patients that need them, adverse environmental impacts due to the use of pharmaceuticals should be minimised. This should be achieved by making the ERA and its consequences mandatory. The backbone of all proposed changes is that environmental impacts due to the use of pharmaceutical products should be transparent and mitigated.**

The legislation needs to clearly define environmental protection goals against which emissions of active substances and environmentally-relevant excipients should be assessed. Protection goals should not only include effects on ecosystems, but also potential effects on human health (including antimicrobial resistance) due to the presence of pharmaceutical residues in (drinking) water, crops (via irrigation with treated wastewater) or fish. This should also include the possibility to derive emission limit values for the active substance if these are needed for manufacturing guidelines (e.g., for antimicrobials see section 2).

It is fully acknowledged that the benefits of medicines for human use to patients practically outweigh the risks to the environment. However, a ground for refusal is needed for mandatory measurements to strengthen ERA. For instance, to ensure a complete and timely ERA and the possibility of mandatory risk mitigation measures, the ERA should become either (1) a stand-alone ground for refusal or (2) part of the B/R balance. Mandatory risk mitigation measures (in case of an identified risk) should go hand in hand with mandatory completeness and timeliness of dossiers, otherwise this could be a disincentive to submit a completed ERA. Risk mitigation measures should be applied for substances or products with adverse environmental impacts, in order to reduce emission of these substances into the environment. These substances should be monitored, using analytical techniques reported by MAHs, and data from monitoring and new scientific data should be used to re-evaluate the ERA at regular intervals, including the

application of risk mitigation measures. The pharmaceutical legislation should be coupled to other environmental legislations to facilitate exchange of monitoring data and risk assessment results. Besides this, conditions of use could be strengthened for substances with a risk, like provisions to not allow over the counter sales or other risk mitigation measures.

A monograph system should be established, with a central repository of quality-assessed ecotoxicity data per substance. Provisions on data sharing should support applicants to provide, share, and use data for their product-based ERA, which will only differ in the calculation of expected exposure based on the use profile of the product. The study results should be available to other stakeholders in the form of endpoints or study summaries (not the complete study reports).

Awaiting the setup of a monograph system, which will take considerable time, an amendment to the current Regulation should provide for a central database of all environmental data for each active substance and the outcome of the ERA and the hazard assessment for each product, such as risk limits (PNECs), classifications (PBT or vPvB) and risk quotients, including results (endpoints or summaries) from the underlying studies. As stated above, summaries cannot be used by other MAHs and thus there should be no confidentiality issues.

Provisions for a catching-up procedure for legacy products (authorised before 2006) are needed to make sure the monograph system contains information for all environmentally relevant active substances. A catching-up procedure should begin with substances that have an identified risk in other legislative frameworks (e.g., WFD) or other prioritisation exercises.

If the ERA is a stand-alone ground for refusal or part of the B/R balance, all decisions on the ERA and RMMs should be the result of harmonized assessment of good quality – there can be no differences in risk mitigation requirements between similar products with the same active substance and their SmPCs should be harmonised. The monograph system, with an associated substance-based assessment, will also be a solution to this. An ERA working party would be the basis for harmonisation and education.

Environmental impacts due to the use of pharmaceuticals may concern more aspects than emissions via wash-off, urine and faeces. This also concerns waste of medicines because they are issued in too large amounts, with vast amounts of left-over medication as a result. Due to short shelf-lives, many pharmaceuticals are discarded before they are even distributed to the patient. Environmental consequences are that more products need to be manufactured and more waste is being produced, which is both unnecessary. From a general sustainability point of view, this concerns not only the active ingredients, but also other materials (e.g., packaging). Regarding the waste management stage, appropriate collection systems are not always in place.

## 2. Greener Pharmaceuticals with respect to antimicrobial resistance.

An Expert Group (EG) was arranged to discuss the issue “Greener pharmaceuticals with respect to antimicrobial resistance”. The EG consisted in XXX members which provided a wide representation of expertise, authorities and nationalities. The EG met remotely several times for the purpose of discussing the issue and drafting this document. This document has also been presented to the GMDP/IWG for discussion. The views to this document of the GMDP/IWG are summarized in the Annex below..

### 2.1 Issues and solutions

The EG concluded on the following:

1. For the purpose of the interpretation of this CP, “greener pharmaceuticals with respect to antimicrobial resistance” should be understood here as the manufacturing of active substances and medicinal products that minimizes or eliminates the emission of substances able to induce or select antimicrobial resistances (AMRs) in the environment. Manufacturing process is thus considered to include waste management and emission monitoring. Reduction can be achieved through benign by design of the API, re-examination of processes and by preventing and minimising the release of APIs to the environment.
2. Emissions of APIs during production are a threat to the environment and public health<sup>11</sup>. For instance, antimicrobials can select for antimicrobial resistance, and local hot spots of emissions from production of antimicrobial API and medicinal products accelerate AMR<sup>12</sup> that can result in loss of efficacy of the medicinal product. The substances able to induce or select AMRs in the environment are diverse (e.g. biocides, metals, antimicrobials, other pharmaceutical active substances), the EG agreed to target this work on antimicrobial substances.
3. The conclusions of the EG will apply to the manufacturers of finished medicinal products containing antimicrobial substances and to manufacturers of antimicrobial substances. Although the scope of this CP focused on human medicines, the EG agreed that veterinary medicines should follow similar rules. The approaches described here could be implemented in a step-wise process to include all relevant APIs.
4. The EG discussed on possibilities to include emissions of APIs outside the scope of the Pharmaceutical legislation. The use of the Industrial Emission Directive 2010/75/EU can also be considered in those manufacturing sites placed in the EU. The pharmaceutical industry is covered by this Directive and respective documents on Best Available Techniques (BREF). It should be noted that these BREFs do not include AMR considerations. The EC should check to include an update of the OFC BREF<sup>13</sup> in the EIPPCB work programme for future BREF reviews. However, in this document, technical issues in BREFs are not pursued further as this is no solution for productions in third countries and equal treatment of products manufactured outside the EEA but marketed inside the EEA is not ensured.
5. Although out of the scope of this Concept Paper, the EC should further investigate whether integrated sustainability concepts could also be part of the environmental risk assessment. In any case, a guideline needs to be developed on how to weigh environmental impact (including other sustainability aspects) in order to compare

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<sup>11</sup> Larsson DGJ. Pollution from drug manufacturing: review and perspectives (2014) *Philos Trans R Soc Lond B Biol Sci* 369(1656):20130571 doi: 10.1098/rstb.2013.0571

<sup>12</sup> Larsson, DGJ and Flach C-F (2021) Antibiotic resistance in the environment. *Nat rev Microbiol.*, 1–13. 4 Nov. 2021, doi:10.1038/s41579-021-00649-x

<sup>13</sup> BAT Reference Document on Organic Fine Chemicals Production

different APIs/products, e.g., to be used for sustainable procurement. This would be in line with the recently published EU Commissions 'Recommendation on the use of Environmental Footprint Methods'<sup>14</sup>.

6. The EG discussed briefly on **technical issues**. Technical issues are out of the scope of this Concept Paper, but the EG wanted to explore them.

Any requisite to the manufacturers would require the development or update of guidelines and guidance documents.

Any guidance document developed, should at least contain Emission Limit Values (ELVs) and to what compartments they should apply. ELVs for substances should protect against the induction of selection for antimicrobial resistances and/or environmental impact. Concerning this concept paper and focus on greener manufacturing of antimicrobials, it is of high importance that ELVs for antimicrobials protect against antimicrobial resistance due to emissions related to manufacturing of active substances and medicinal products. Antimicrobials can also have an impact on the environment (e.g. cyanobacteria or plants); in cases when the environment is more sensitive, the ELV may need to be focussed on both protecting the environment as well as minimizing AMR which is in line with the AMR Industry Alliance<sup>15</sup> approach. The ELV would be unique for each substance.

Currently, resistances in the environment are neither part of the Environmental Risk Assessment (ERA) nor of any other part of the authorisation dossier and there is no accepted methodology for the determination of ELVs. Some attempts to derive ELVs can be found in the published scientific literature and industry has already published proposals for those values (Tell *et al.*, 2019, Vestel *et al.*, 2021, Bengtson-Palme & Larsson 2016, Rico *et al.*, 2017)<sup>16</sup>. Nevertheless, the acceptance of any ELV would require first a careful assessment by regulators of the methodology followed.

Once a methodology is agreed, the individual ELVs should be determined for each substance used as an API. This could be done using several sources of information: Authorities, the scientific community, industry associations (e.g. for existing antibiotics), as a part of the ERA for the newly authorised products, as a part of the ERA within the catching-up procedure and during re-evaluating the ERA (see part I of this concept paper). The determination of ELVs should also at least comprise a discussion on sampling points, sampling protocols and sampling frequency. This has to be considered in the new legislation and cross-references are needed here.

Besides the ELVs, any guidance document produced should also discuss other technical issues related to in-house processes: Process redesign to lower the emission, treatments of effluents to diminish/eliminate emission, etc.

A number of pharmaceutical companies are trying to address the topics of ELVs for antibiotic substances, e. g. Industries AMR Alliance framework on manufacturing. Those companies also call for a level playing field and clear regulatory requirements. It

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<sup>14</sup> Commission recommendation on the use of the environmental footprint methods to measure and communicate the life cycle environmental performance of products and organisations. C(2021) 9332 final

<sup>15</sup> [https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR\\_Industry\\_Alliance\\_Manufacturing\\_Framework.pdf](https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf)

<sup>16</sup> Vestel *et al.* (2021). "Default Predicted No Effect Target Concentrations for Antibiotics in the Absence of Data for the Protection Against Antibiotic Resistance and Environmental Toxicity". doi: 10.1002/ieam.4560

Tell *et al.* (2019). "Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations". <https://doi.org/10.1002/ieam.4141>

Bengtsson-Palme, J. and D. G. J. Larsson (2016). "Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation." *Environ Int* **86**: 140-149.;

Rico, A., *et al.* (2017). "A probabilistic approach to assess antibiotic resistance development risks in environmental compartments and its application to an intensive aquaculture production scenario." *Environ Pollut* **231**(Pt 1): 918-928.

would appear to be in the interest of pharmaceutical companies to have a working system to address the issue of AMR in the environment, also with the aim to safeguard the effectiveness of the antimicrobial substances they produce.

7. The EG discussed on **operational issues** (i.e. how can the public administration address the emission of antimicrobials to the environment from manufacturing sites). Three approaches were discussed. Some of them would require developing new guidelines or amending existing documents to include an AMR perspective.

The approaches discussed by the EG were the following:

- a. To **emphasise existing GMP (Good Manufacturing Practices) guidance** that applies to the production of antimicrobials outlining points for manufacturers and inspectors to consider in preventing AMR.

Description:

Although current EU GMP does not cover environmental controls, there are elements of GMP that should require good control of raw materials, processes and waste that could be emphasised more with respect to preventing AMRs. WHO has already started working on concepts to consider emissions to the environment in GMP<sup>17</sup>, which is a good starting point for developing the relevant processes. Leverage on the current EU GMP with the following objectives:

- Raise awareness among manufacturers, GMP inspectors and inspectorates of the existing WHO GMP guidance<sup>18</sup> that applies to the production of antimicrobials and the control of the supply chain.
- Raise awareness of options for reducing and mitigating the uncontrolled disposal of waste and wastewater containing antimicrobials, with a focus on the role of current GMP in this.

Impact on EU pharmaceutical legislation: No formal impact as applies to existing GMP. Interpretative guidance should be developed.

Advantages: It could be implemented relatively quickly by industry stakeholders. Industry would already be familiar with the GMP guidance and there would be no new requirements. .

Disadvantages: Without changes in legislation, it is not possible to enforce. Requirements are non-binding, ELVs cannot be demanded or controlled. New interpretation of existing requirements could lead to disputed inspection outcomes. It is arguable that environmental issues are within the scope of the current GMP. Equal treatment of European and other producers is not ensured, because third country authorities may have different legal and regulatory frameworks for control of waste and wastewater.

- b. To include **new environmental requirements** with respect to AMR in the **legislation related to medicinal products for human use and the Good Manufacturing Practices (GMPs)**

Description: If emission/discharge control were connected to GMPs this would allow control of the whole production chain. Therefore, a revision of the GMP Guideline is required. This could be achieved through the introduction of a modified definition of GMP into Directive 2001/83 where a reference is made to a new legal act on emissions/discharge. The Commission should be given the task to establish Emission Limit Values (ELVs) in a separate legal act (delegated or implementing), in the section below referred to as article xx. Non-compliance by a manufacturer to the emission limits set in a separate act as proposed above would mean non-

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<sup>17</sup> WHO Technical Report Series, no. 1025; Annex 6: Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance; 2020

compliance to the GMP standards. With emission and discharge limits as a part of the GMP definition, manufacturers in third countries would in practice also be legally bound to the regulation on emission limits if they want to produce medicinal products or active substances for the EU/EEA. Through the connection to the current GMP legislation, a framework for regulatory control and action, in case of violation on the rules, would be available. In order to avoid overlaps with other legislation (e.g. environmental legislation), the control should focus on APIs.

Amendments should be done in Directive 2001/83 but also in Commission Delegated Regulation 1252/2014 (GMPs for active substances) and Commission Directive (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569 (GMPs for medicinal products for human use) as well as in guidelines connected to this legislation. A standard (e.g. defining sampling points or frequency, description of a suitable monitoring program) could also be developed in a later stage. Implementing a standard and certificate is anticipated to facilitate the work for all stakeholders. More detailed technical guidance on management responsibilities, preventive actions or measures in production, sampling methods and plans, analysis, control of the supply chain will need to be defined. Legal powers may need to be provided to inspectors to carry out official sampling when necessary.

At least the following amendments should be done in Directive 2001/83 (suggested amendments in italic text). Implementations might start at specific timepoints defined in legislation.:

- A new definition in article 1 is suggested in order to widen the scope of the GMPs to cover emission of substances able to induce or select AMRs in the environment: *“Good manufacturing practice: The part of quality assurance which ensures that medicinal products and active substances are consistently produced, imported and controlled in accordance with– the quality [and emission] standards appropriate to their intended use, including the requirements that follow from the legal act referred to in article xx.”*

This is the definition of Good manufacturing practice according to the definition in Commission Directive 2017/1572 with an added reference to the suggested new article in Directive 2001/83 pointing to a legal act (article xx) on emission limits for active substances able to induce or select antimicrobial resistances (AMRs) in the environment. The new definition should be combined with a transitional provision stating that the part pointing to the new legal act (article xx) on emissions should not enter into force until the new legal act is in place.

- A new article (article xx) on emission/discharge limits is also suggested: *“The Commission shall be empowered to adopt delegated [implementing] acts [in accordance with article 121a] to set Emission Limit Values for active substances.”*  
The delegated [implementing] acts should initially focus on antimicrobials in accordance with the scope of this Concept Paper. However, by not specifying in article XX the group of active substances for which ELVs should be determined, additional pharmaceuticals or groups of pharmaceuticals may be added in delegated [implementing] acts should additional environmental concerns different from AMRs arise.
- To give the option to refuse applications of marketing authorisation Article 8.3 k), that stipulates what documents the application for market authorisation shall be accompanied by, should also be amended according to the following: *“A document showing that the manufacturer is authorised in his own country to produce medicinal products and also, when the application concerns a substance included in the act referred to in article xx, a document showing that the manufacturer and the*

*manufacturer of the active substance meets the requirements in the mentioned act.* This requirement should also be reflected in Annex I.

- Or as an alternative to the suggested amendment of Article 8.3 k): Revise Article 8(3) ha “A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice *and meets the requirements that follow from the legal act referred to in article xx.*”

If article 8.3 (ha) is altered, amendments should also be done in Article 46 f) according to the following: “to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use only active substances, which have been manufactured in accordance with good manufacturing practice for active substances *and meets the requirements that follow from the legal act referred to in article xx* and distributed in accordance with good distribution practices for active substances...”

The requirement in 8.3 (ha) should also be reflected in Annex I.

- If amendments are made in article 8.3, depending of choice of amendment, additional amendments in article 118.2 could be done. Article 118.2 in Directive 2001/83, that regulates when the marketing authorization should be suspended or revoked, could also be amended, for clarification reasons, according to the following: "In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with. *This may also be the case when the requirements in the act referred to in article xx is not fulfilled at manufacturing of a medicinal product that contains a substance that is covered by the act.*”

In addition to the changes described above: The Regulation 1252/2014 (GMPs for active substances), the Directives (EU) 2017/1572 and (EU) 2017/1569 (GMPs for medicinal products for human use), EudraLex Volume 4 (GMP guidelines) and ICH Guideline Q7A GMP for Active Substances would also require revision and amendment.

Advantages: Clear and equal rules applied in the EU and abroad. Existing structures can be used. Level playing field between producers in and outside the EU. Significantly reduced emissions of antimicrobial APIs are anticipated. The act on emissions (article xx) will be legally binding and can be changed if new information is provided from MAA, environmental authorities or other sources. The information provided in the act on emissions would be valuable for GMP inspections.

Disadvantages: Will require additional resources from national competent authorities. New competences should be developed by inspectorates. In countries with a Mutual Recognition Agreement covering GMP and equivalence of supervising systems, the impact on the MRA should be assessed.

### c. **Declaration of compliance** with an environmental standard.

Description: During the marketing authorisation procedure, the marketing authorisation applicant should provide a declaration assuring that the manufacturers (finished product and API) comply with certain legally binding environmental standard that could include ELVs (see below). The standard could be developed by an independent organisation or regulators. The standard should include at least relevant ELVs, measures to minimize emissions to the



environment and a description of a suitable monitoring program of emissions at the site of discharge to the environment. Waste includes all waste, for example liquid and solid, as well as substandard batches. The responsibility of ensuring compliance lays on the applicant. The declaration should be issued and updated regularly, for example every third year subject to review. ELVs should be included in the standard only if this approach is used as a stand-alone option. As an alternative the declaration could be used as a documentation at GMP-inspections according to suggestion b above if both options (B and C) are considered in the legislation.

Impact on EU pharmaceutical legislation: The Directive 2001/83 should require amendment to include this additional requirement. This should be placed in the article 8 and/or the Annex I of the current Directive.

- Article 8.3 k) should be amended according to the following: “A document showing that the manufacturer is authorised in his own country to produce medicinal products *and also, when the application concerns an active substance that is covered by [the environmental standard] a declaration issued by [a third party/ authority/ applicant] showing that the manufacturer and the manufacturer of the active substance meet the requirements in [the environmental standard].*

Because of this, amendments should also be done in Annex I. The suggested amendment of article 8.3 k) above should be applicable if approach C is used as a stand-alone approach. Further amendments may also be necessary with respect to ELVs in the standard, for instance there could be an article about ELVs in the Directive, see approach B above. Also in this approach, amendments could be made in article 8.3 ha) as an alternative amendments of 8.3 k).

Advantages: Equal treatment of products marketed in Europe. Emission limit values could be changed if new information is provided from MAA, environmental authorities or other sources.

Disadvantages: May require additional resources. If not implemented as a part of the documentation within GMP inspection there would be difficulties for the enforcement, i.e. how to ensure compliance. In that case effects on reduction cannot be controlled or followed.

- 6) Any of these approaches may have an impact on availability and affordability of medicines. The implementation of new processes, the modification of those already existing, the creation of protocols, sampling procedures, etc., would have a cost for manufacturers and would require a period of implementation that cannot be oversight. Manufacturers not complying with e.g. GMPs cannot be accepted. Therefore, sufficiently long and appropriate transition periods should be introduced with the new regulations in order to prevent supply problems with active pharmaceutical ingredients.
- 7) Whichever measure is taken to limit the emission of antimicrobials to the environment they should not have an impact on the quality of the finished product or active substance.
- 8) The expert group considers a change of the concept and definition of the manufacturing process, both for APIs and medicinal products, to include also waste treatment of APIs as an important point regardless of approach. The suggested approaches have different pros and cons, and different possibilities for enforcing that APIs and medicinal products are produced with little or no risk of AMR due to manufacturing both within and outside of the EU. There may be additional pros and cons to the approaches described here. It could be a possibility to use more than one approach.

## 2.2. Concluding remarks on section 2

The EG agreed that the emission of APIs and medicinal products as well as antimicrobial APIs and medicinal products from manufacturing sites is a public health and environmental concern<sup>18</sup> that should be addressed wherever it is produced. The selection of AMRs in the environment can also have an indirect role on the availability of efficacious antibiotics. Therefore, the EG supports that clear rules for manufacturers are set in order to limit the emission of antimicrobials to the environment.

The EG agreed that manufacturers and importers of APIs and Medicinal Products should be responsible of ensuring that the emission of antimicrobials from manufacturing sites does not have an impact on the selection of AMRs or the environment and that this should be confirmed by applicants or by marketing authorisation holders.

The EG agreed that any of the approaches above could have an impact on availability and affordability of human medicines. However, it has to be weighed against the fact that AMR already today costs lives and has a societal and an economical burden that is anticipated to increase<sup>19, 20</sup>. The need to reduce emissions of antimicrobial substances during production is further underpinned by the One Health approach as well as several goals within the 2030 Agenda for Sustainable Development.

The issue should be addressed both at EU and worldwide scale which is in line with the provision of the pharmaceutical strategy that also stressed the need for international cooperation.

The provided proposals have different impacts on the reduction of emissions to the environment. The strongest impact has a combination of option B (changes in GMP) and C (declaration of compliance). Both require changes in the EU legislation for the implementation of ELVs in legislation or in a respective guideline. Furthermore, GMP guidelines have to be revised and declarations of compliance have to be checked within authorisation procedures and can be used for control of GMP compliance. There is still a high impact on emission reduction by choosing only option B. Option C alone does not require any changes of GMP guidelines, but still changes in legislation for implementing ELVs. However, the compliance of this approach would be difficult to ensure, and additional provisions may be needed. Option A (emphasise of the existing GMP guidance) would not require an amendment of the pharmaceutical legislation, but in this approach the compliance is voluntary and it does not ensure a level playing field between manufacturing sites in Europe and outside the EU. Therefore, the impact of option A might be too low and legally binding measures have to be further pursued. However, irrespective of the revision of the legislation, support of the EU to the process initiated by WHO as first step is recommended. An acknowledgement of the WHO initiative could be included in the recital of the legislation. To address the issue globally, the pharmaceutical legislation, including the GMP legislation, need to be amended.

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<sup>18</sup> E. g. Larsson, D. G. J. (2014). Pollution from drug manufacturing: review and perspectives. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369(1656), 20130571

Thai et al. (2018) "Occurrence of antibiotic residues and antibiotic-resistant bacteria in effluents of pharmaceutical manufacturers and other sources around Hanoi, Vietnam". doi: 10.1016/j.scitotenv.2018.07.126

Miao et al. (2021). "Abundance and Dynamic Distribution of Antibiotic Resistance Genes in the Environment Surrounding a Veterinary Antibiotic Manufacturing Site". doi: 10.3390/antibiotics10111361

<sup>19</sup> [Jonas, O. B., et al. \(2017\) Drug-resistant infections: a threat to our economic future \(Vol. 2\) : final report \(English\). HNP/Agriculture Global Antimicrobial Resistance Initiative Washington, D.C. : World Bank Group](#)

<sup>20</sup> Murray CJL et al (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, Jan 19, 2022. DOI:[https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

However, it is acknowledged that the main task of the GMP legislation is still to assure a high quality of medicinal products.

Whichever approach(es) is (are) decided, implementation could follow a step-wise approach.

Transitional arrangements may be necessary in order to avoid undesired impacts of the availability of medicines in the market.

## **Annex. Views from the GMDP/IWG on the second part of the Concept Paper (Greener Pharmaceuticals with respect to antimicrobial resistances)**

The part of the Concept Paper (CP) related to “Greener pharmaceutical with respect to AMR” was circulated on the 31<sup>st</sup> of January 2022 to the members of the GMDP-IWG for written comments. Besides, the CP was taken for discussion to the 105<sup>th</sup> plenary meeting of the GMDP-IWG (08/03/22) in order to get the views of the Working Group on the part of “Greener pharmaceuticals with respect to AMR”. This Annex reflects the views gathered from the GMDP-IWG.

- 1) The GMDP-IWG is of the opinion that GMPs should not be used to tackle environmental issues because:
  - a. Conceptually, GMPs are a tool developed and designed to guarantee a certain level of quality of the products manufactured. Including environmental considerations in GMPs is a deviation from that already complex principle.
  - b. Inspectors’ expertise and competence is related only to manufacturing aspects linked with quality.
  - c. Inspection coverage of manufacturing sites abroad is very resource demanding; widening the scope of GMPs will significantly increase the workload for inspectorates.
  - d. EU/EEA manufacturers should comply with the widened GMPs, while third country manufacturers would be inspected by their own NCA, MRA partner or PIC/S. Therefore, adding environmental standards to GMPs might potentially result in an imbalance in inspections that could compromise EU manufacturers’ competitiveness.
- 2) The GMDP-IWG considers that the burden of ensuring compliance with these environmental standards should not lay on the Inspectorates, but on marketing authorisation holders and manufacturers.
- 3) Considering all that, **the GMDP-IWG supports the option c above** (i.e. Declaration of Compliance with a certain environmental standard) provided that the implementation of this approach is not linked to GMPs.
- 4) The GMDP-IWG considers that the Declaration of Compliance should cover both manufacturers of API and finished product, for both veterinary and human medicines
- 5) Besides the three proposals already detailed in the CP, the GMDP-IWG would like to make an additional one related to importing limitations for antimicrobial APIs:
  - A mandatory audit of the manufacturing site in a 3<sup>rd</sup> country is needed covering the environmental aspects. The audit is required by the Marketing Authorisation Holder or by the pharmaceutical company importing the antibiotic product or API to EU/EEC area.
  - In addition to GMPs this audit could include compliance with certain environmental standards, and the auditor would need to have training/competence on environment area
  - Audit frequency may be identical to current GMP audit frequency i.e. 3 years, or even higher if necessary (e.g. 2 years). The audits need to be mandatory for both human and veterinary APIs and products (current veterinary legislation allows risk-based GMP audits for veterinary APIs).
  - The QP declaration (already a requisite during the marketing authorization of new HMPs) could be widened to include an environmental evaluation.

## **Appendix. First year results of the IMI-PREMIER project (Sept 2020 – Sept 2021)**

Active ingredients from medicines can be released into the environment through a variety of routes, and once there they may prove harmful to wildlife and ecosystems. In the EU, since 2006 new medicines are required to undergo an environmental risk assessment (ERA). However, few of the approximately 1900 active pharmaceutical ingredients (APIs) marketed before 2006 have been assessed for their environmental impact.

The aim of PREMIER is to deliver a framework for assessing and characterising the environmental risks of APIs. This framework will be used to prioritise and screen older ('legacy') APIs that have never been evaluated in an ERA. The assessment tools developed in PREMIER may also be used to pick up potential environmental risks of new APIs that are still under development, thereby contributing to greener drug design. PREMIER will make environmental data gathered within the context of the project visible and publicly accessible to all stakeholders.

The major achievements within the first year of the project are listed below:

WP1 (Prioritisation and environmental assessment of APIs): The universe of APIs available on the European Market was mapped, and easily accessible data of (authorization) studies relevant for environmental risk assessment (e.g., identifiers, physico-chemical characteristics, toxicity data) were collated in spreadsheets. From this list, the first test candidates were selected after grouping the APIs based on working mechanism and selecting those groups with the lowest number of toxicity data. In order to minimize fish testing, a decision tree was developed to determine whether toxicity testing in fish is likely to result in new and useful information.

WP2 (Exposure and effect tools): Two computer models have been developed: a physiologically-based pharmacokinetic model (PBK model) for fish, and a model to predict API levels in European surface waters, called ePiE. The fish PBK model serves to predict the uptake, distribution, metabolism and excretion (ADME) of APIs in fish. Unique features of the model are its generic nature and easy parameterisation (making it very useful for risk assessment purposes), and the fact that it accounts for ionization of APIs. The expanded ePiE model is being used internally (i.e., by consortium members) to predict the concentrations of specific APIs in European surface waters in order to establish the validity of the model predictions and to identify potential environmental risks of specific compounds. We are currently preparing publications on the expanded ePiE model and the fish PBK model so these become available to the broader scientific community.

WP3 (API information and assessment system): The PREMIER database architecture and digital assessment system (DAS; the software that lets us analyse the data) have been created and established. Two planned update releases have already taken place this year which are available to all consortium members. The first collection of data was loaded to the database and is now available to all partners to be utilized for scientific purposes. This includes a preliminary list of APIs on the European market (based on EMA's Article 57 database) and part of the ERA data from the iPiE database. The database and DAS will be open and publicly accessible to all stakeholders by March 2023 (M30).

WP4 (Guidance and application; Green pharmacy): Interviews were held with stakeholders (WP4.1) and industry drug discovery and development experts (WP4.2). Results of these interviews were analysed and used as input for two sets of separate workshops for these WPs. A background paper on 'Pharmaceuticals in the Environment – Understanding the Feasibility

of Designing Greener Drugs' was written. Results of an internal workshop on criteria how to identify more environmentally friendly APIs were integrated in a draft scientific paper.

WP5 (Management, Communication and Dissemination): Efforts have concentrated on establishing the project governance and management structure to optimally coordinate from the scientific and operational point of view all the project activities. This included the strategic scientific coordination, the formation of the scientific advisory board, the planning and support of regular project meetings, the monitoring and of the progression of tasks, deliverables, milestones and potential risks. From the communication side, WP5 established an editorial team, developed a project communication plan (D5.2) as well as various communication materials and platforms. Also, a sustainability group was set up and the first draft of the sustainability principles were defined.

The project has gained a lot of experience with the collection, extraction, selection and curation of ERA data on APIs and making these available; for now, mainly within the consortium. One of the lessons learnt is that APIs can be referred to using different identifiers, e.g., their common name, CAS number, chemical structure, ATC code, medicinal product, etcetera. All these identifiers refer to products that can have slightly different specifications such as salts, enantiomers, prodrugs and mixtures. From an environmental risk perspective, it is the active moiety (or moieties) in the environment that is of main interest and this active moiety is not always adequately covered by traditional identifiers. One recommendation of PREMIER to the stakeholder community, and particularly regulatory authorities such as EMA, OECD and WHO, is to introduce a unique identifier for environmentally active moieties in order to facilitate the management of ERA data and the subsequent risk assessment process. The introduction of such an identifier would for example facilitate the extraction of API consumption data from sales data on medicinal products. This recommendation is now actively propagated towards stakeholders, e.g., during EMA's Veterinary Big Data stakeholder forum which was held online on June 1-2, 2021.

Another example of an early impact of the PREMIER work is the application of the expanded ePiE model in two ongoing studies, i.e., one on the antidepressant amitriptyline and one on the NSAID drug ibuprofen; both initiated by industry. In both cases, the ePiE model was used to predict API concentrations across European surface waters in order to obtain an impression of the exposure and associated risks, including the identification of hotspots. Two manuscripts are currently being prepared. Regarding ibuprofen, a follow-up study is being considered focussing on identifying optimal locations for the installation of tertiary treatment facilities to reduce environmental risks, underlining the potential of ePiE as a tool for scenario study and the optimisation of interventions. Both examples illustrate that the tools developed in PREMIER are already being used by stakeholders to determine the extent to which APIs pose a risk to the environment and to identify cost effective measures along the development-production-use-emission-effect chain.

Other tools and initiatives being developed include a decision tree for performing fish testing in WP1.3 (with the aim to avoid these vertebrate studies where possible and reduce it to the absolute minimum where necessary), the public release of the PREMIER database (anticipated for March 2023), read-across approaches, QSAR models and other tools to describe and predict sorption, biodegradation, bioaccumulation and ecotoxicity.

## 10. Concept paper for EC on **Reuse of animal data**

**Main theme:** Upgrading of existing regulatory concepts to avoid duplication of animal studies and facilitate reuse of data.

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic lead	Experts from EMA
Drafting Group	Experts from SWP and EMA

## Background introduction

Under the current framework, abridged marketing authorisations (i.e. generics, hybrids, biosimilars) and informed consent applications can rely on the non-clinical studies conducted for the reference medicinal product, as far as they are relevant. However, for stand-alone applications (Articles 8(3) or 10b), the animal study results can only be reused if publicly available in the literature, and once the data exclusivity has expired, unless applicants have entered into commercial agreements. If the non-clinical results were not published or available through commercial agreements, the applicants must repeat studies already performed, even if they are not expected to bring any new scientific information.

The possibility to reuse non-clinical data is therefore conditioned to:

- 1 – the availability of the results in the literature or public domain
- 2 – the (expiry of) data exclusivity or any commercial agreements between companies

In practice, regulators often observe unnecessary repetition of animal studies which could be avoided by applying some changes in the legislation, as commercial agreements cannot be enforced.

In addition, it should be highlighted that animal studies are not solely included in Module 4 of eCTD, but they are also included in Module 1 as part of the environmental risk assessment (ERA), which can never be referred to regardless of the legal basis chosen by the applicants.

The proposals made in this concept paper focus on solutions to facilitate the reuse of animal study results:

- included in Module 4. This would mainly affect stand-alone marketing authorisation applications: Article 8(3) for a known active substance and Article 10b for fixed-combinations. Article 10a (well established use) and 10c (informed consent) applications do not require to provide study results and rely solely on the literature and on the dossier of the original product, respectively.

- conducted as part of the ERA and included in Module 1. This would benefit all marketing authorisation applications with a known active substance, regardless of the legal basis chosen by the applicants. Of note, proposed changes on the ERA are also covered, to the relevant extent, in the concept paper 9 on environmental challenges.

## **Recommendations for change**

### **1. Transparency of non-clinical data**

Despite the 3R principles being introduced into EU legislation, several impediments still lead to unnecessary repetition of animal studies.

- The first impediment to tackle is the fact that, contrary to clinical trial results, pharmaceutical companies have no obligation to publish non-clinical studies, irrespective of whether they have supported a marketing authorisation application, or whether the development of the concerned medicinal product has failed.

The lack of transparency of non-clinical results is the first hurdle to the reuse of these results. Progress in science depends on previous observations and experiments, as well as on the dissemination of correct and reliable knowledge. Therefore, making non-clinical results publicly available would not only prevent the repetition of investigations, but would also:

- ✓ improve research and scientific knowledge
- ✓ support consistency in methodology and comparability of data;
- ✓ facilitate cross-product learning through pattern recognition;
- ✓ enhance scientific understanding on safety data which cannot be retrieved from clinical trials such as reproductive toxicity, carcinogenicity and genotoxicity findings; and
- ✓ improve the overall safety of medicinal products and other chemicals in the environment.

The publication of non-clinical study results for an active substance can be valuable to support further developments of the same active substance or the development of new active substances from the same class, without unnecessarily repeating animal studies.

For central marketing authorisation applications, EMA has a policy in place to publish the final assessment reports (or the latest available reports in case of withdrawn applications) in English language, which detail the conclusions on the non-clinical part. However, this information is not systematically published for national marketing authorisation applications (or at least not in English). In addition, when a company discontinues the development of an investigational medicinal product prior to MAA submission, non-clinical data collected until then are not made publicly available either.



Transparency of non-clinical results, including for failed developments, is key to prevent repetitions of animal studies for product candidates, similarly to transparency policies of clinical trial results.

- Secondly, some animal studies are conducted to support the ERA (e.g. fish studies), and are included in Module 1.6 of the eCTD, which is a requirement regardless of the legal basis chosen by the applicants. It is acknowledged that in vivo ERA studies are available for many active substances according to the current state-of-the-art procedures and there would be no need to repeat those studies if those results were considered relevant and made available to future applicants of known active substances. ERA data deriving from animal studies should also be published to facilitate the reuse of these data and meet the 3R principles.

The considerations presented in this concept paper are without prejudice to any patent restrictions that could exist in the context of medicinal products for which the non-clinical part of the dossier is hereby discussed (patent limitations are considered outside of the remit of this paper and are, thus, not discussed).

### **1.1. Proposed solutions – in legislation**

It is proposed to amend the legislation and enforce the publication of animal studies. Different solutions were explored:

- **Adding a provision to establish a database for the publication of non-clinical study results** similarly to what was introduced in the Clinical trial Regulation (EU) No 536/2014:

*"(67) Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.*

*(68) For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential."*

The group considers this proposed requirement should apply after completion of the MAA review similarly to what is mentioned in the above-mentioned Clinical Trials Regulation (Regulation (EU) No 536/2014). It might be further considered whether it is possible to also impose this requirement of publication in case the company decides to terminate the development of an active substance. The publication of non-clinical data should be done irrespective of data exclusivity (see section 2) but taking patent protection considerations into account.

**Pros:** the requirement to publish the data would be the MAHs' responsibility - as already done for clinical trial results; this would then be easier to implement.

**Cons:** additional resources to establish and maintain a database would be required and it might impact on commercial interests of companies, as the data would be made public with a view to be reusable by anyone without commercial agreements.

- **Adding a provision to establish** detailed monographs including non-clinical and environmental data (e.g. results of fish studies) for new active substances, and, retrospectively, for known active substances similarly to what is done within the PREMIER

project in the context of ERA. Data contained in these monographs should be collected in a standardised data format, comparable to the CDISC Standards for Exchange of Nonclinical Data (SEND) for non-clinical data and CDISC SDTM for ERA data.

Such a database of monographs could allow different levels of information: in addition to make the conclusions publicly available, it would be possible to also release the full non-clinical reports upon consent of the data owner. Such monographs would be publicly available, and the results could be reused by applicants if considered relevant for their medicinal product developments. For example, information deriving from animal studies as part of the ERA could be reused without requiring generating new environmental fate and ecotoxicity data.

**Pros:** it could improve transparency while facilitating commercial agreements between companies.

**Cons:** there is a risk of duplication of work (assessment of non-clinical data as part of initial MAA and harmonisation of outcome per active substance afterwards); the responsibility and burden to harmonise and publish the conclusions would be on the regulators. Drafting monographs on all medicinal products/active substances already assessed would be time-consuming.

Transparency and publication of non-clinical data in a database or via a monograph system would not only support the reuse of animal data in the context of pharmaceuticals, but would also allow other areas such as the chemical and food sectors, where an overlap in terms of regulatory assessment exists, to benefit from such published information. In this context, the "one substance, one assessment" initiative in the frame of the EU Chemicals Strategy for Sustainability (involving the European Commission as well as EU Agencies such as ECHA, EFSA, EEA and EMA) is in line with this proposal. However, it should be noted that the data format in which the study reports are being currently submitted to EMA might not necessarily be compatible with formats used by other EU agencies. Therefore, care should be taken to develop a common reporting format and to ensure that the methods and results are presented in a comprehensive enough manner so that they can be reused.

## **1.2. Proposed solutions – in guidance**

It is proposed to develop a practical guidance document containing information regarding the use and access to the new database.

## **2. Regulatory data protection on studies performed in animals**

Public availability of non-clinical results on its own would not be enough to tackle the unnecessary repetition of animal studies if those data cannot be referred to in subsequent marketing authorisation applications, due to data exclusivity or absence of legal provision to reuse these data.

### **➤ Animal study results included in Module 4**

For abridged applications (i.e. generics, hybrids and biosimilars), the applicants can refer to the Module 4 of their reference products, after expiry of data exclusivity, when the data are considered relevant to support the new marketing authorisation application. Therefore, these applications are not expected to repeat animal studies, unless this is required from a scientific perspective (e.g. to support a new route of administration).

However, for non-abridged MAAs such as full-mixed MAAs (Article 8(3)) or fixed dose combinations (Article 10b), applicants can be requested to repeat studies already performed by other MAHs in the context of previous submissions for the same active substance. This happens when the study results are not available in the public literature (see part 1 of this concept paper) or because the published

studies are still protected by data exclusivity, which prevents the reuse of this literature for regulatory purposes. As stated in Section 6.1.6 of Chapter 1 of Volume 2A of the Notice to Applicants:

*"As long as a product authorised in the EU is under data exclusivity, the reliance on published or unpublished pre-clinical and clinical data contained in the dossier of that product within the EU or in third countries by the competent authorities to grant a marketing authorisation would lead to a circumvention of the data exclusivity rules".*

It must be highlighted that some of the animal studies requested are not only duplicated and therefore against the 3Rs principle (Directive 2010/63/EU), but also do not provide any meaningful and additional information on the safety characterisation of the active substance, which has already been evaluated in the previously authorised non-clinical dossier.

In general, data contained in Module 4 is being released in its totality under "Access to Documents" procedures pursuant to Regulation (EC) No 1049/2001, when applicable. The rationale for releasing this information is that most of what is reported in Module 4 is not considered commercially confidential information (CCI) and therefore would not harm the economic interests of the originator. This is also stated in the EMA/HMA guidance on the identification of CCI ([link](#)) which states that "*non-clinical information is not considered per se as commercially confidential*". However, Section 6.1.6 of Chapter 1 of Volume 2A of the Notice to Applicants states that "*During the period of data exclusivity of a medicinal product, the data contained in the pre-clinical and clinical file of that product and obtained through access to documents or freedom of information legislation within the EU or in third countries, cannot be relied on by other applicants or the authorities in a subsequent application to ascertain the safety and efficacy of other products*".

This highlights how animal data, despite generally not being considered CCI (under the EMA policy on Access to Documents), is not allowed to be reused during the period of the data exclusivity for the sole purpose of providing a regulatory and commercial advantage to the MAH, which had to bear the respective costs for research and development.

To evaluate the impact in terms of reuse of animal data, it should be noted that MAAs for known active substances under Article 8(3) (full-mixed), and article 10b (fixed dose combinations) of Directive 2001/83/EC represent approximately 10% of all MAAs submitted to the EMA under Regulation (EC) No 726/2004.

#### ➤ **Animal studies included in the ERA**

An ERA may entail the carrying out of specific animal studies (e.g. studies in fish). Since the ERA is part of Module 1 (CTD M1.6), when the exposure in the environment is high enough to trigger the need to perform ERA studies, applicants of abridged applications (i.e. generics, hybrids, biosimilars) cannot refer to the reference product's results and are required to repeat animal studies, even if they are not expected to show any new additional information. This systematic repetition of animal studies is not in line with the 3R principles and is not cost/time efficient. This topic was also further developed in the concept paper on ERA.

## **2.1. Proposed solutions – in legislation**

### **NON-CLINICAL (MODULE 4)**

The current rules for data exclusivity for studies performed on animals should be reconsidered in order to facilitate the reuse of those data as much as possible.

Excluding Module 4 from data exclusivity would avoid Competent Authorities to request duplication of animal studies for the sole purpose of addressing a regulatory requirement without bringing any new

scientific evidence on the safety and efficacy of medicinal products. This would apply mainly for stand-alone marketing authorisation applications (Article 8(3), Article 10b) for a known active substance, as abridged applications would await end of data exclusivity on the clinical module.

The group discussed if only safety data within Module 4 should be excluded from data exclusivity. However, based on the content of Module 4, it is difficult to define, on a general level, which studies could support the safety of the medicinal product. Potentially, any study in Module 4 could have an impact on safety and this can only be verified on a case-by-case basis. Therefore, it is recommended to consider the whole Module 4 as not covered by data exclusivity.

Since developing a database as proposed in section 1.1 might take several years, in the meantime, it is proposed that any applicant should be allowed to have access to non-clinical data, regardless of whether they are made publicly available in such a database or come from Module 4 from another MAH obtained through Access to Documents or from published literature. The relevance of those data in the context of MAA would be a matter of scientific assessment.

It is therefore proposed to:

- **Add a legal provision** to avoid (or even prohibit) the need to repeat non-clinical in vivo studies with known (active) substances to support a MAA, if no further evidence is expected, by modifying Directive 2001/83/EC. This is anticipated to have an impact for full-mixed marketing authorisations under article 8(3) and fixed dose combinations under article 10b.
- **Allow the reuse of published non-clinical data** included in the literature or detailed safety monographs or non-clinical databases or obtained through Access to Documents (see section 1.1 above), regardless of the legal basis of the original product authorisation as long as patent protection considerations are fulfilled.
- **Amend the legislation** to clarify that the data exclusivity would not apply to non-clinical data. The relevance of granting a year of data exclusivity under Article 10(5) on the basis of significant non-clinical studies would need to be reconsidered. It could be proposed that such year of data exclusivity could be granted solely on the basis of a new indication supported by significant clinical studies only (this is the case in the vast majority of cases granted).

In the context of reuse of published animal data, the group also discussed the possibility for applicants submitting a dossier for known active substances to refer to EPARs of other products containing the same active substance. However, it was agreed that these summaries do not contain the enough detailed information to support a MAA under Directive 2001/83/EC in line with what reported in the notice to applicants (section Volume 2A).

The removal of data exclusivity for non-clinical studies included in Module 4 would not change the way in which regulators will assess a MAAs. Every study proposed by the applicant and required by legislation will need to be assessed to ensure that the quality of the data is acceptable and up to the standards (e.g. in accordance with OECD TGs and GLP principles) required to support a MAA, in line with the current scientific knowledge. The fact that a study has already been endorsed and submitted in a previous application will not automatically ensure an endorsement of the data and waive the need to conduct further studies if scientifically justified. The "reused study" or "reused data" will need to be reassessed in the context of the new application to ensure there are no data and safety gaps. Requests for scientific advice on the adequate reuse of non-clinical data should be encouraged to satisfy requirements for Module 4 without repeating unnecessarily animal studies.

## **ERA (MODULE 1)**

Directive 2001/83/EC should be amended to allow applicants of abridged applications to refer not only to pre-clinical studies and clinical trials, but also to the reference medicinal product's ERA studies. In

the context of generics the following amendment to Article 10(1) should therefore be considered: "*By way of derogation from Article 8(3) **(ca) and (i)**, and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of **environmental studies**, pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Union*".

The relevance of in vivo ERA studies performed to support the MAA of the reference medicinal product to support hybrid/biosimilar applications should be assessed on a case-by-case basis, similarly to the rest of the non-clinical studies.

In the context of Article 10(3) of Directive 2001/83/EC the following amendment should be considered: "*In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate **environmental studies**, pre-clinical tests or clinical trials shall be provided*".

In the context of Article 10(4) of Directive 2001/83/EC, the following amendment should be considered: "*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate **environmental studies**, pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided*".

Similarly the same approach should be proposed for stand-alone MAAs with a known active substance by clarifying the requirement in Article 8(3)(ca) or in Annex I of Directive 2001/83/EC.

## **2.2. Proposed solutions – in guidance**

A guideline to promote the reuse of available animal data in line with the 3R principles would be considered highly useful to complement the amendments of the legislation proposed in section 1.1 of the present concept paper. The guidance document would contain some recommendations on the aspects to consider for the relevance of animal data that could be reused and for regulatory options available (e.g. Scientific Advice) to discuss the possibility of relying on previous data in order to apply for a MAA.

Notice to Applicants Vol. 2a and 2b should be amended accordingly.

## **3. Misuse of animals**

Some MAA dossiers submitted via the centralised procedure propose the repetition of animal studies for the same objective or redundant studies on excipients or active substances with well-known toxicity, even if not required by the regulatory authorities.

The European Directive on animal welfare (2010/63/EC) stated in this context that the use of animals for scientific purpose should be reduced as much as possible due to ethical reasons. However, this Directive states that these requirements only apply to the user of the animals (e.g. the test facility where the studies are conducted, mostly CROs), not to the sponsors of the studies. Therefore the legal

provision to enforce compliance with 3R principles should also apply to Applicants (irrespective of potential subcontracting agreements with Contract Research Organisations (CROs)), as it should be their legal responsibility not to repeat animal studies which have not been required by regulatory authorities. Currently, even if misuse of animals can be reported in the assessment report during the evaluation of a MAA by highlighting an experimental approach which is not in line with the 3R principles, there is no legal or regulatory consequence for such misuse.

Additional studies performed by applicants because of different regulatory requirements in various ICH regions are outside the scope of this concept paper. However, harmonisation of study requirements at ICH level would be beneficial in order to avoid repetition of animal studies.

### ***3.1. Proposed solution - in legislation***

It is proposed to include in the legislation the obligation for the applicant/MAH to comply with the 3R principles and to ensure that their subcontractors also meet these obligations by only performing animal studies for medicinal products' development when strictly necessary. This will support regulators when commenting/questioning animal studies that were performed without being in line with the 3R principles in the assessment report.

### ***3.2. Proposed solution - in guidance***

Of note, some MAHs might have an obligation to repeat animal studies to fulfil requirements in other regions. Therefore, harmonisation of non-clinical requirements, endorsement of the 3R principles and reuse of animal data should be attempted at ICH level to maximise the impact of the new measures proposed.

As proposed in the section 2 above, Scientific Advice on the proposed non-clinical development should also be encouraged to avoid misuse of animals and non-compliance to the 3R principles.

### **Information out of scope – measures in the US to facilitate reuse of animal data**

After approval of a New Drug Application (NDA) or Biologics Licencing Applications (BLA), the summary of the assessment report (equivalent to EPARs) are published proactively on the FDA website, with a highest priority for New Molecular Entities (NME), then non-NMEs. Non-clinical reviews of approved applications are not proactively published on the FDA website but are released under the equivalent to Access to Documents, for transparency reasons, after redaction (of confidential commercial information).

In addition to stand-alone applications (NDA and BLA where a consent to refer to data conducted by another company would be required to reuse these data), we have been informed that the FDA has a specific legal basis that allow an applicant to rely on data (including non-clinical) generated by another company, without their consent: new drug application developed pursuant to section 505(b)(2) of the FD&C Act. According to the FDA, a section 505(b)(2) application contains full reports of investigations of safety and effectiveness, but at least some of the information required for approval of that application comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. There is no correlate to the 505(b)(2)-type pathway for biologics license applications, so this legal basis seems to be only possible for chemicals.

We understand that the scope of the concept paper excluded considerations on changes to legal bases therefore the possibility to create a new legal basis for MAAs in order to facilitate reuse of animal data was not explored by the expert group.

## 11. Concept paper for EC on Functioning of the centralised assessment procedure

**Main theme:** Simplification and streamlining of business processes with regard to elements influenced by the basic legislation; improving transparency and openness. Facilitating access of innovative medicinal products to patients

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic leads	<i>Experts from EMA</i>
Drafting group:	Experts from CHMP, CAT and EMA

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# Recommendations for change:

## 1. Refusal to validate and/or early termination

### Problem statement

- **Currently, absence of a legal basis for a scientific invalidation and of an explicit legal basis for administrative validation (i.e., more explicit than current language in Article 6.3 of Regulation (EC) 726/2004)**

The CHMP and the network is currently experiencing resource constraints to face the increased demand on EMA committees and NCAs. There is an increased need for the CHMP and network to manage more efficiently and effectively the use of resources for the evaluation of applications. It is thus necessary to avoid use of resources for applications with manifest (scientific) deficiencies and missing documentation that would not allow for a proper scientific evaluation of the application.

**Currently the framework only allows invalidation on purely administrative grounds and even only to a limited extent (cf. below referred court cases) but it is not possible for regulators to invalidate applications when the application is (scientifically) immature** and when it is foreseeable that the applicant will not be able to address the deficiencies within a reasonable timeframe (i.e. unpredictable re-start of procedure, short timeframe for assessing often new studies results), nor to terminate an application earlier than day 80<sup>1</sup>.

Having to assess such applications under the current framework results in an inefficient use of the network resources. In addition, such limited scientific evidence does, in principle, not support a proper assessment of the benefit/risk balance. It should also be emphasised that, even if the regulatory authorities flag potential deficiencies of an application to an applicant at an early stage (e.g. during scientific advice, pre-submission meeting), some applicants nevertheless proceed with the submission of their application despite the identified major deficiencies which the authorities under the current framework have to validate.

**Furthermore, in recent proceedings before the General Court, doubts on EMA's own power to invalidate a MAA under Article 6.3 of Regulation (EC) No 726/2004 have been flagged, even for solely administrative grounds.**<sup>2</sup>

The relevant legislative provisions, read in combination with the court cases referenced below, clarify the purely administrative nature of validations and the remit of the Agency when validating marketing authorisation applications:

- Commission v France (Case C-145/11), in which it was held that the purpose of the validation procedure was to ensure that the formal requirements of the application for marketing

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<sup>1</sup> Article 6, Regulation (EC) No 726/2004

*'The duration of the analysis of the scientific data in the file concerning the application for marketing authorisation must be at least 80 days...'*

<sup>2</sup> Articles 6(3), Regulation (EC) No 726/2004:

*"The Agency shall ensure that the opinion of the Committee for Medicinal Products for [Human/Veterinary] Use is given within 210 days after receipt of a valid application"*

For Orphan designation: Article 5(4) of Regulation (EC) No 141/2000:

*"The Agency shall verify the validity of the application and prepare a summary report to the Committee. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application".*

authorisation are fulfilled. More specifically, the Court held that the validation stage was designed to ensure the completeness of applications. However, the validation stage did not permit any substantive evaluation / any substantive assessment of the documents and particulars submitted.

- *Shire v EMA (T-80/16)*, in which the General Court found, again in very similar terms, that the verification by EMA of the validity of applications is purely administrative in nature.

As a consequence, only 2 initial MAAs (out of a total of 410 between 2019 - Jul 2021) submitted via the centralised procedure resulted in a negative validation outcome due to the data protection period of the chosen reference medicinal product not yet being expired. In addition, a total of 31 initial MAA had the validation suspended for a period of up to 2 months in order to address validation questions and 6 initial MAAs have been withdrawn by the applicant while the validation was still ongoing.

Of note, the new Veterinary legislation [Regulation EC No 2019/6](#) includes a specific article on applications and a validation step has been included. Please refer to Article 6 paragraph 4, 5 and 6<sup>3</sup>.

The same reflections could be considered for marketing authorisations procedures under Directive 2001/83/EC.

## Proposed solutions – in legislation

- **More explicit legal basis for administrative validation**
- **Introduction of an explicit legal basis to invalidate applications on scientific grounds**
- **Introduction of an explicit legal basis to stop “premature applications” at an early stage**

In order to give a clear remit to regulatory authorities to perform an administrative validation, a more explicit legal basis is advisable. In order to support the completeness and usefulness of the ‘administrative’ validation, the list of dossier requirements for initial MAAs that are legally required and that need to be fulfilled should be updated building on the elements foreseen in article 8(3) of Directive 2001/83/EC. In addition, the list of requirements needs being further developed, to include additional elements, e.g., the need for CE certificate/NB opinion, GMP certificates (there will be a need to reflect different scenarios). Of note, such list can be included as an annex to regulation (EC) No 726/2004.

As per article 6(6) of the revised veterinary legislation, a specific legal basis could be provided that determines that failure to comply with such legal requirements within a defined timeframe will result in the withdrawal of an application.

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<sup>3</sup> Vet Regulation:

*“... 4. The applicant shall be responsible for the accuracy of the information and documentation submitted with respect to its application.*

*5. Within 15 days of receipt of the application, .... the Agency, ..., shall notify the applicant as to whether all the information and documentation required in accordance with Article 8 have been submitted and whether the application is valid.*

*6. Where .... the Agency, ..., considers that the application is incomplete, it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.*

Clinical trials regulation 536/2014, Article 5, paragraphs 3, 4 and 5 states “Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned”. Same for substantial modifications in Article 17...”

Furthermore, EMA and CHMP / CAT support the introduction of **an explicit legal basis and a specific mechanism to prevent premature and low-quality dossiers to be validated and/or discontinued before exhaustion of the 210 days.**

Such mechanism should allow EMA secretariat subject to approval of the Rapporteur and endorsement of the CHMP/CAT to assess whether data package in the dossier supporting the application is adequate to conclude on the benefit/risk balance of the medicinal product: determine the extent and type of deficiencies (including quality of raw data when required) and consider the significance of the missing and/or incomplete application and its impact on the assessment of an application, taking into account the medicinal product concerned, the proposed indication(s) and the time required to address such identified deficiencies. The level of involvement of the Rapporteur and the CHMP/CAT will need to be defined through guidance. Involvement of CHMP/CAT is, in particular, important in case of invalidation based on scientific grounds and in addition will foster consistency. Based on such scientific review in case of significant deficiencies, EMA should **have the right:**

- 1) **to invalidate on scientific grounds** (beyond the current administrative grounds) and refuse the start of a procedure, if any key data for the start of an assessment by CHMP/CAT are identified as missing at validation stage; **and**
- 2) **to stop at an early stage the scientific assessment**, even potentially before reaching day 80 milestone, in the event of major deficiencies in the application emerging from the assessment after the start of the procedure.

The introduction of an explicit legal basis<sup>4</sup> should come with **a mechanism for the applicant to obtain predictability** from the regulators on the adequacy of their data package for the assessment of the B/R before filing their application, without prejudice to the applicants' right of defence but also striking a balance with the need of an expeditious resolution and of a more efficient use of CHMP/CAT resources.

## **Proposed solutions – in guidance**

### **Implementation of a mechanism:**

- **to stop at an early stage the scientific assessment of an application due to scientifically premature (incomplete) applications**
- **to enable pre-screening before submission**

In order to support the implementation of the mechanism to stop (administratively and scientifically) incomplete applications and give predictability to the applicants, the legislation should mandate the EMA to develop a guideline on the invalidation and early termination principles and criteria. Consideration should be given to the need and modalities of involving the Rapporteur(s) or the CHMP/CAT when implementing the mechanism in respect of premature applications. As highlighted above, agreement with Rapporteur and endorsement by the CHMP/CAT is, in particular, important in case of invalidation based on scientific grounds.

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<sup>4</sup> In EMA's views, achieving this result in respect of premature applications, after validation, would appear possible by way of interpretation of the current relevant provision of the Regulation. However, the introduction of a more explicit legal basis is recommended to prevent unnecessary confrontation and legal disputes with disappointed applicants.

## 2. Enhanced work sharing assessment in the EU

### Problem statement

- ***Resource capacity within the network for assessment of centralised applications***

The current multinational assessment team (MNAT) concept was introduced to allow an assessment team to be formed from assessors coming from different national competent authorities (NCAs) and allows payment by EMA secretariat to the individual NCAs of the assessment team, as not all NCAs have the resources and expertise available to conduct the full assessment. The multinational collaboration has allowed to maximise the use of available resources and expertise within the network and facilitates participation of national competent authorities in assessment allowing for expertise to be built up, while maintaining the high-quality scientific assessments of the scientific committee.

Despite the existence of this practice, the network is still facing major resource-capacity issues, which have become even more pressing with the COVID-19 crisis. There are currently important resource constraints within the network, resulting in huge difficulties to take on assessment of centralised applications either as rapporteur, Co-Rapporteur or part of the assessment team. The network highlighted that this resource capacity problem should not be considered in isolation from the update of the EMA Fee Regulation (ongoing simultaneously).

In addition to the discussion on additional resources to increase assessment capacity, there is a need to consider opportunities for changes into the current system of assessment to cope with the workload and avoid delays due to the difficulties to allocate Rapporteurship and to support Rapporteurs in selecting expertise in composing the assessment team, in particular in specific complex and innovative area.

It is important that the EU authorisations for medicinal products remains competitive as compared with other referenced authorities worldwide, in particular regarding the timelines of approval.

It is therefore proposed to facilitate the involvement of additional resources in case of difficulties to form an assessment team, with relevant additional expertise.

**Options for consideration to expand the assessment team** are as follows:

- **External experts**

Involvement of external experts to an NCA in the assessment is currently possible and in the remit of NCAs when constituting their individual assessment teams. However, some NCAs face limitations when constituting their assessment teams, e.g., to find out a particular expertise, no possibility to remunerate experts and/or face limitation in the choice of experts available in their territory. Nevertheless, addition of external experts may still be of limited impact considering the difficulties of finding available experts. Also, experts have limited knowledge of the regulatory requirements needed to perform an assessment, therefore appropriate training would need to be provided.

- **EMA staff**

Due to limitations of expanding the resource capacity with additional external experts, the possibility for EMA staff to take part in the assessment team should be considered for evaluation of applications submitted through the centralised procedure or referred to EMA committees.

Such EMA role in the assessment can range from enhanced process support/coordinating task (which is possible without revision of the legislation) to performing assessment as part of the assessment team under the accountability of the Rapporteur.

Enhanced support from EMA staff in the assessment process may be welcome such as a more coordinating role in case of MNATs and act as a quality manager overall for the reports.

Regarding an assessment role, it could be considered that EMA staff could contribute to the assessment dossier as part of the assessment team e.g., in situations where none of the NCAs can provide relevant expert to be nominated in the assessment team of the Rapporteurs. This option would imply some policy decisions in the role of the EMA in support of the network.

Taking the above considerations into account, an expansion of the concept of assessment team is necessitated to address the difficulties of allocating Rapporteurship by increasing the pool of available experts which would facilitate the formation of assessment teams.

## **Proposed solutions – in legislation**

In order to facilitate the resource and expertise capacity there is a need to include specific legal provisions to enable a more efficient, agile and robust assessment team concept for the centralised procedure, providing the opportunity to call upon additional experts, including EMA staff,<sup>5</sup> whenever required and to provide adequate measures to resolve the current difficulties when allocating rapporteurship.

Notably it was highlighted by the network that what can be the potential foreseen role of EMA staff expert in the assessment will need further reflections as this is an important policy change. It will need to be considered for instance, the extent of the contribution, in which circumstances EMA could contribute (e.g., when no relevant expertise is available at national level? For specific procedures?), accountability (e.g., assessment activities under the supervision of the Rapporteur(s)). This may be part of a more global policy discussions on the resources of the network and fee-generating activities.

## **3. Support to innovation**

### **3.1. Scientific advice**

#### **Problem statement**

Scientific innovation poses challenges to the medicines regulatory framework which often finds itself unprepared to address them. This is currently evident in relation to medicine-device combinations, especially ones involving digital devices implying the use of novel, i.e., digital, endpoints and ways to conduct clinical studies, i.e., remotely or in a decentralised manner and use in combination with a companion diagnostic. The problem is most evident during drug development when the innovative technologies have their first contact with regulatory authorities. Moreover, current EMA activities related to innovation should connect better to formal regulatory interactions (scientific advice) and novel, prior unforeseen expertise (e.g., software experts for digital devices) should be made available more readily when and as necessary. Also refer to section 3.3, Scientific advice for PRIME.

#### **Proposed solutions – in legislation**

- Proposal for a **legal basis to engage with various stakeholders**, as applicable, as part of scientific advice (without mention of specific stakeholders in legislation) which can cover for the following activities/stakeholders:

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<sup>5</sup> In addition to the “technical, scientific and administrative support” currently awarded by the legislation.

- 1) scientific advice in parallel to a joint scientific consultation with the co-ordination group for HTAs,
- 2) parallel scientific advice with the Medical Devices Coordination Group (MDCG) expert panels, the device competent authorities and/or, if it would become applicable, notified bodies (or any other governance structure which could provide scientific advice on medical devices)
- 3) scientific advice involving some governance structure relating to clinical trials (e.g. CTFG) so as to allow more informative advice on clinical trial applications and hence more integrated development advice.

Ideally, relevant legislative provisions should remain high-level to allow flexibility in their implementation and adaptability over time based on scientific progress.

- Proposal for a **horizon scanning activity** to be foreseen in legislation and a **regulatory sandbox** (for developments challenging the current regulatory framework). It can be an experimentation clause or provision in legislation which provides a structured framework for regulatory experimentation to enable the testing of innovative technologies, products, methods or approaches that deviate from the existing regulatory framework. The sandbox will only be used where this deviation is necessary, appropriate, in the interests of public health and under multi-stakeholder supervision, ensuring that appropriate safeguards are in place.

## **Proposed solutions – in guidance**

Relevant guidance to implement the above legislative proposals would be needed.

Regarding horizon scanning, in its implementation other initiatives such as at the NCA and HTA level will be considered.

### ***3.2. Rolling review***

#### **Problem statement**

For innovative products, the Accelerated Assessment needs often to be reverted to standard timelines due to the need for long clock-stop for the applicant to provide final study results and to address major deficiencies in the underlying marketing authorisation dossier supporting the application under assessment. Currently there is no mechanism for the applicants and regulators to closely engage in a pre-assessment of the data along their generation and the product development. There is a need for a more flexible system to facilitate the evaluation of certain applications and truly accelerate the assessment/authorisation phase. In addition, it has been observed that EU authorisations for medicinal products take often longer as compared to the other referenced authority worldwide. The COVID-19 pandemic has exemplified the need for more adaptive tools such as the rolling review, as one of the regulatory tools that EMA uses to speed up the assessment of data as they become available from ongoing studies for a promising medicine. The rolling review process has shown to effectively prepare for the authorisation phase to be shortened including the decision-making process.

It is understood that the current rolling reviews for COVID-19 medicinal products with very tight deadlines and constant submission of documentation is extremely demanding and, as a consequence, has taken a lot of the NCAs capacity, resulting in not being available to take onboard other products' Rapporteurship.

Recognising the benefits of this regulatory tool while acknowledging the challenges it presents under the current pandemic, it is considered that under the revised framework, this tool - in view of its

benefits - should receive an explicit legal basis but should be designed as exceptional and limited and two **options should be considered** either:

A. to **products for emergency situations only** or

While it is agreed that this continuous (pre-) assessment type of approach is indeed valid in emergency situations for instance, for the assessment of vaccines and treatments for COVID-19 (and already a possibility), it is reported that at the level of the assessment, this is a very demanding, time- and resource-consuming procedure.

It was reported that implementation beyond emergency products would be very difficult (e.g., in terms of workload, team's availability, difficulties for work-planning, etc).

For medicinal products addressing other unmet medical needs, it was pointed out that there are available tools in place (accelerated assessment, CMA, etc) which should be enough to facilitate/accelerate the approval of these medicines. It was reported that the resources underlying the rolling-review would not be proportionate and would not lead to an optimal resources' allocation to the detriment of other product activities.

B. to **products for emergency situations and products with a high public health impact**

While acknowledging that rolling review can be a very demanding process under pandemic situation, there is a need for a more flexible system to facilitate the evaluation of certain applications beyond emergency products, in particular for medicinal products addressing a high unmet medical need such as truly game changer medicines and/or certain PRIME products.

Although recognising the challenges experienced with the rolling review model used for COVID-19 medicinal products, it is emphasised that this was happening due to the particular time pressure linked with the pandemic situation. Therefore, a rolling review framework outside a pandemic context should be framed with standard timelines and stable data packages so that it can be sustainable for the system. The vision could be a kind of 'ATMP certification-like' process to pre-assess under standard timelines a data package when reaching a meaningful stage, to allow early and gradual identification of deficiencies and facilitate / accelerate their resolutions progressively as the application is being complemented with the required data (but not resulting in a certification). As a result, this would enable a fast-track authorisation procedure at the level of the MA application.

## **Proposed solutions – in legislation**

The proposal is **to introduce in the regulation the concept of rolling review**, with subsequent **shortened/accelerated MAA phase** including the decision-making process, which if to go beyond emergency medicines, should as a prerequisite follow standard timelines and data packages.

When moving forward with this proposal, the model would need to be further elaborated e.g. in terms of scope, conditions and modalities at the level of guideline.

## **Proposed solutions – in guidance**

Once the concept has been enshrined in legislation, the model would be better framed and detailed in guidance rather than in legislation to allow modalities to evolve alongside with emerging science and public health needs.



### **3.3 PRIME**

#### **Problem statement**

##### ***Lack of legal basis for PRIME in the pharmaceutical legislation***

The PRIME scheme has been launched by the Agency to enhance support for the development of promising medicines that target an unmet medical need, through enhanced interaction with developers. It is currently the only scheme offered at EU level to foster enhanced development support and is currently available on a fully voluntary basis. EMA has published recently an analysis reviewing the first 5 years' experience of operation of the EMA's PRIME scheme.<sup>6</sup>

The fact that it is not reflected in the regulatory framework, means that in situations of capacity constraints of the Agency and/or Network, such as the present situation of COVID-19 pandemic, activities with a legal basis and timeframes have to be prioritised over PRIME, with a potential detrimental impact in supporting access of promising products to patients and loss of competitiveness of the EU regulatory system.

##### ***Accelerated assessment for PRIME products***

The expectation with PRIME is that enhanced regulatory and scientific support during development will lead to a regulatory evaluation within an accelerated assessment framework, with reduction of the overall timeframe from 210 days to 150 days.

Whilst the vast majority of PRIME products have started their regulatory review under accelerated assessment (17 out of 19) and PRIME has resulted in a slightly higher success rate in terms of maintenance of AA vs non-PRIME products (44% vs 35%), a significant proportion of PRIME applications still reverted to standard timetable (approximately 56%)<sup>7</sup>. This shows that there is room to optimise current interactions to support the necessary knowledge acquisition throughout development and thus facilitate accelerated assessment. Furthermore, there are currently no means for regulators to ensure that the application is mature enough/addresses relevant points discussed during development at the time of submission of the marketing authorisation application.

##### ***Scientific advice for PRIME products & strengthened dialogue with International regulators***

Considering that the main means for enhanced support to PRIME products during development is through scientific advice, it is key to have the necessary flexibilities in place to allow for e.g. rapid advices to be provided, if needed and in duly justified cases, so as not to negatively impact the development of PRIME products.

Considering that in most cases PRIME products are developed globally and would benefit from convergence of regulatory requirements with International Partners to speed up development and access to patients, strengthened dialogue with International Regulators should be prioritised for PRIME products. This takes account of the outcome of the surveys conducted both by the Agency and Trade Associations with a strong call for strengthened dialogue with International Partners.

##### ***Interaction with HTA bodies for PRIME products***

With products in the PRIME scheme by their very nature addressing an unmet medical need it is important that an enhanced focus is given throughout the decision-making chain leading to access to

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<sup>6</sup> [5-year report on PRIME](#)

<sup>7</sup> Analysis of applications (PRIME vs non-PRIME) started under accelerated assessment with a CHMP opinion between 01/01/2018 and 30/06/2021

patients. At present the PRIME scheme exclusively expresses a commitment from the European regulatory network to provide enhanced development support and later accelerated review. Given that the evidence generated during development also has to address the needs of down-stream decision makers such as HTA bodies, the conduct of parallel scientific advice would be desirable. Experience has shown however that the HTA network does not consider the PRIME designation in their prioritisation criteria. Equally, there should be enhanced cooperation between regulators and HTAs at time of this is making, facilitated through the new HTA Regulation.

## **Proposed solutions – in legislation**

Regarding legislative changes, the three following options should be considered:

### **A. PRIME linked to incentives**

- As reflected in the Pharmaceutical Strategy for Europe, the Agency supports the proposal to incorporate PRIME in the regulatory framework so as to accelerate product development and authorisation in areas of unmet medical needs; in addition, it should be considered to expand the scope to cover both regulatory and HTA support by including in the future HTA Coordination Group under the new HTA Regulation as participant in the decision making for PRIME eligibility requests.
- Consider whether accelerated assessment could be reflected in the legislation as an expected incentive for PRIME products, provided that the application is deemed mature enough around the time of submission of the MAA to undergo accelerated assessment review; this could be established at a specific 'submission readiness meeting.' Any such approach should ensure that regulators continue to have the means to refuse to start under accelerated assessment if, necessary conditions are not fulfilled.
- Reflect in the legislation possibility of rolling review to be applied for certain PRIME products expected to be of high impact on public health (cf. section 3.2 on rolling review); PRIME designation should however not result in an 'automatic' entitlement to rolling review, but follow the criteria defined for eligibility to rolling review; the accumulation of knowledge by the Rapporteur team during the development phase, including planning for post-authorisation evidence generation, which is particularly relevant in the context of a conditional marketing authorisation is of particular relevance to enable a successful review under accelerated assessment.

### **B. High-level reference to PRIME framework without a reference to specific incentives, such as accelerated assessment or rolling reviews beyond emergency use.**

Notably, many CHMP and CAT members expressed reservations on PRIME and related activities (e.g., rolling review, accelerated assessment). The enhanced support to PRIME products requires additional resources from the regulatory network and the actual value is not yet considered established but currently the experience is very limited also it is acknowledged that it is difficult to judge in terms of its relevance at this stage.

For the reasons explained above under topic 3.2, some CHMP and CAT members are of the view that PRIME products should not fall within the scope of rolling review. Lastly, the idea that PRIME products could ask for rapid advices is not supported. Reduction of timelines by few weeks does not appear 'key' in the proposed context and will put unnecessary pressure to the system. Further, it is questioned in which forum it could be discussed if not during SAWP meetings.

If the concept of PRIME or "enhanced support to innovation" were to be included in the legislation, it is the view that the proposed legislative provision should be kept at very high-level. The scope and other details should be left open, to allow later changes without revision of the legislation.

### C. No legal basis for PRIME

Given all the reservations reflected above and the fact that the tools on which PRIME scheme relies are already existing in the legislation, it was even strongly expressed by some CHMP and CAT members that including a legal basis for PRIME at this stage is questionable.

### Proposed solutions – in guidance

- Introduce as part of PRIME guidance documents, the possibility for regulators to engage with Applicants prior to the submission of a PRIME MAA to ensure that the application is mature enough/addresses key points discussed during development and hence can be assessed in an accelerated timeframe. This could be done through means of a final (pre-submission) kick-off meeting.
- Reflect in guidance on scientific advice, possibility, in duly justified cases, of flexible and rapid scientific advice for PRIME products, based on experience with COVID rapid SAs.
- Reflect in guidance on scientific advice, prioritisation of parallel advice with international regulators for PRIME products to facilitate global development.
- In the implementation of the new HTA Regulation, 1/ reflect in supporting guidance that the criteria for Joint Scientific Consultation should in principle be applicable to developments with “PRIME designation”, and 2/ make “PRIME designation” as explicit entry criterion for voluntary Joint Clinical Assessment during the incremental phase until full application, unless the product is anyway covered by the mandatory requirements (oncology, ATMP and – in step 2 – orphans).
- Consider review of current accelerated assessment timetable for ATMPs (120+30 days), as it makes it challenging to keep products under accelerated assessment.
- Update of AA templates with consideration for ATMP-specific templates (to be considered as part of the actions from the Quality toolbox survey).
- Consider the possibility of involvement of patients/HCP in the unmet medical need determination at the timepoint of PRIME eligibility and/or during regulatory review by CHMP/CAT (e.g. discussions on conditional marketing authorisation).
- Consider fee structure for simple, rapid turnaround advice provision.
- Ensure that any changes to the definition of unmet medical needs currently under discussion in the context of review of the orphans and/or paediatric legislation encompass PRIME and conditional marketing authorisation as well.

### ***3.4. Pre-submission phase: End of phase 2 meeting / End of proof of concept***

#### **Problem statement**

Recent discussions with developers have identified the potential benefit of enhanced stewardship by regulators throughout the development. Currently there are multiple entry points for applicants to the EMA. Companies may apply for orphan status, they may or may not apply for centralised scientific advice, and they will be required to submit a paediatric plan. With the introduction of CTIS, the Agency will also begin to have visibility of the planned clinical trials.

While the paediatric regulation introduced a system that allows the network to influence the development plan for products in paediatrics, in the current set-up, there is a fragmentation that does

not allow to put together a more holistic picture of the planned development of a product in adults, let alone be able to influence and steer it.

By contrast, the FDA holds End of Phase 2 (EoP2) meetings with nearly all applicants for initial marketing authorisation applications; this allows for a complete review of the product at an early stage, when the company is about to embark in their registration programme. During EoP2 meetings all aspects of the product development are discussed – quality, nonclinical & clinical - whether the company has questions or not.

While there is a resource investment in setting up and holding these meetings, it allows to front-load the assessment on certain aspects of the product (e.g., quality aspects and/or toxicology) leading to less resources being required during the NDA process. Most importantly, however, it does give the FDA an opportunity to steer the development of the product and ensure that the companies “get it right first time”. This results in potentially less intensive resource during the authorisation procedure.

The proposal is therefore for a new legislative framework that would allow EMA to also hold meetings with companies before they invest in their registrational programme, akin to the EoP2 meetings. This would allow the network to have visibility of the development programme of a product after end of phase 2 or proof of concept and, at the same time, the ability to ensure companies are encouraged to prepare a data package that would be suitable to support the proposed indication.

It is estimated that currently around 70% of applicants of initial MAA have come for centralised SA on their development plans. While this is of course welcome, it also means that one third of companies do submit MAAs without having engaged with us. In addition, the current scientific advice system means that discussions are only focussed on items that the companies bring forward for discussion, rather than a more holistic view of their plans for the dossier.

## **Proposed solutions – in legislation**

It proposed to include in the legislation the requirement for the applicant to have a meeting with the EMA after end of phase 2 or proof of concept for all MAAs or a subset e.g. new active substances.

It could be focussed to a determined number of applications (e.g., for unmet need) or widely applied to all MAA. The intended scope of this requirement would exclude applications for generic and biosimilar products.

This proposal could be viewed as an extension of the current scientific advice system, with a view to bring a better connection between fostering development and performing the assessment of products.

One fundamental difference between the FDA’s remit and that of this proposed legislation, is that FDA also approves clinical trial applications, and has therefore tighter checkpoints to ensure that companies follow the advice given. In the EU system, it is understood that clinical trial approvals would remain the remit of national competent authorities. Nevertheless, the applicant would have to declare the advice received and justify any departures when submitting their CTAs.

This proposal could also be linked with a “refusal to validate” should the company submit the MAA with a data package that did not follow the recommendations given. This could give predictability at time of submission to the applicants on the (non-)acceptance of their MAA. This would only be applicable if the approach was applied to all MAA, not only to a subset. This would also ensure that network resources are directed toward applications that have the necessary data packages to support the claimed indication.

For the benefit of this pre-submission scientific support, it would be ideal to have continuity in the involvement of the rapporteur from the early-stage pre-submission activities to authorisation phase, at

least under the same conditions and circumstances previously agreed with the European Ombudsman offices for PRIME products. A further extension of those instances would need to be discussed thoroughly with all relevant institutions during the legislative process.

Finally, while there would be resource implications with the implementation of such a system and fee compensation would need to be considered for this activity, the hope is that this new approach would address some of the resource issues in the Network by allowing for a stronger scientific support of companies from an earlier stage, which would result in more robust applications.

The proposal was discussed with CHMP and CAT.

The CHMP did voice some concerns. In particular, there were concerns regarding:

- The workload associated with the proposal and the lack of clarity regarding who would be responsible for the advice (i.e. CHMP vs SAWP). In the case the responsibility were to sit with CHMP/CAT rapporteurs, there was concern regarding the current position of the Ombudsman. There were also some concerns as to the value of this interaction, given that most companies agree their development plans with FDA and nevertheless submit MAAs prematurely.

The CAT do not support the concept of EOP2 meetings. In particular, there were concerns as follows:

- The different legal and regulatory framework between EU and US which questioned the translation of FDA procedures to Europe. To illustrate also the difference in overall review resource allocation - in the USA a reviewer gets assigned to an IND and follows the product/procedure to BLA unless organisational reasons demand otherwise. As such, for example from the quality perspective, there is a phase I review followed by annual updates until the end of phase II meeting by the same reviewer (though with division sign off). Similarly for the other disciplines there is a continuous review. At the EOP2 meeting, the assessor therefore needs little additional time to prepare.

In addition, the entry threshold to clinical trials and development tends to be lower in the USA (partially due to the fact that no upfront GMP inspection is required) and it is at EOP2 that "serious development" is starting. In Europe, the threshold is higher earlier on.

From a specific ATMP perspective, the following points are raised:

- o ATMPs already have the option of the certification procedure for quality and non-clinical
- o A large proportion of ATMPs is already in PRIME, they tend to follow accelerated development with even phase I data being leveraged as pivotal. Even with a more flexible approach to "end of phase II" it would be difficult to pinpoint the right time. Additionally, for PRIME products a second meeting (kick-off) will be introduced.
- o Due to the acceleration, most developments have significant manufacturing changes during phase III and the benefit of a EOP2 meeting is therefore questionable.

From a general perspective CAT raised the following points:

- o That the applicant would have to declare the advice received and justify any departures when submitting their CTAs is not supported. Deviation from a scientific advice, or EOP2 meeting consensus cannot be leveraged as a reason to deny the approval of a clinical trial. The suitability of the data generated for a MAA is not a concept included in the Clinical Trials Regulation. In addition, clinical trial approval is in the remit of member states in Europe, as referenced in the briefing, in contrast to the FDA which is responsible for both the IND and MAA stage.

- Duplicating efforts for very similar purposes is not meaningful and increasing the burden for globalised developments where regulatory convergence is sought by interaction of regulators on other levels.
- Rapporteurs would need to be assigned prior to the EOP2 meeting, increasing the time to MAA and therefore raising uncertainties on whether the products would actually make it to MAA and the planning of resources for the time when they actually do come for MAA for the Rapp/CoRapp.
- If the concept of the EOP2 meeting is based on the review of the entire dossier at the time, the resources needed by no means compare to that of a scientific advice, and, as outlined above, in contrast to FDA, it would be an assessment from scratch. This resource demand would need to be financed. In addition, even considering that the current pandemic situation has put the system under duress, it is not easily envisaged that that amount of resources could be freed up in a post-pandemic setting.
- The idea of reduced resource need at MAA would only materialize, if few changes are made between EOP2 and MAA. This is questioned, not only for the quality, but also for the clinical dossier.
- In case the EOP2 meeting is considered conceptually as pre-assessment, the procedure would have to be routed through all relevant EMA groups, which further increases the resource demand. Even so, at MAA there is input from multiple other parties e.g. CoRapp and other committees who will not have evaluated the details during the EOP2 stage.
- The need to see what is going on in development will be more easily satisfied by the now running CTIS system, which contains details and documents on all trials in Europe and also now has product identifiers that track products during name changes.

In light of all the perplexities expressed by several Committee members, further discussion on this proposal would be welcome.

## **Proposed solutions – in guidance**

If the proposal is agreed, the model will have to be developed in more detail (for example in terms of roles and responsibilities of the various committees, SAWP and EMA in this early engagement with companies, including consideration of potential involvement of the CTCG chair) and in connection with other proposals that may be pursued further for the revision of the pharma legislation.

### **3.5 EU – Emergency Use Authorisation (EU-EUA)**

#### **Problem statement**

In pandemic situation, it is of importance for the public health to have a more agile regulatory tool in addition to the existing conditional marketing authorisation and the article 5(3) scientific opinion that showed limitations. This tool, that would translate in a unified scientific assessment and legal act at EU level, could allow to adapt the requirements for data and administrative requirements to a medicinal product in order to allow an early use of a new medicinal product or indication outside a clinical trial in an emergency situation. The acceptability of potentially more limited data would be balanced by more limited validity of such authorisation (only during the emergency situation with possible further limitations).

The emergency use authorisation will allow faster access to medicinal products for human use based on an EU-wide assessment and scientific position, resulting in an EU regulatory authorisation in times

of urgent unmet medical need. In a global environment, such an earlier EU endorsement would help to secure and deploy certain medicinal products related to the public health emergency, before companies are in a position to submit a formal marketing authorisation application or extension of indication application.

## **Proposed solutions – in legislation**

It is proposed to have a legal basis to introduce the framework of EU-EUA.

This tool of a EU-EUA is aimed at providing swift regulatory decisions at EU level to temporarily permit the supply and use, under certain conditions, of an unauthorised medicinal product, or the supply and use of a medicinal product for a new therapeutic indication not covered yet by a marketing authorisation, in response to public health emergencies.

Such tool should allow **more flexibility in the required format and content of the scientific evidence** which is typically required for a formal marketing authorisation/new indication application for a medicinal product and would strike a balance between the need for sound scientific evidence and timely access.

It should also allow **adaptation of the level of scientific requirements** for the formal MAA application and their evaluation in lieu of a systematic and standardised approach. This **tailored evaluation** would be conducted taking into account the type of product and the intended use, the type and magnitude of the effects observed in terms of efficacy and safety, the burden of disease associated with the emerging health threats and possibly also other factors such as the availability of alternatives.

It should also **allow waiving certain other legal requirements that would be required for a formal marketing authorisation** (e.g., with respect to the Paediatric Regulation, environmental risk assessment, manufacturing or importation authorisation, or labelling), which may not be proportionate to the emergency of the situation. It would furthermore allow a risk-based approach toward compliance with Good Manufacturing Practices (GMP) requirements that is currently not possible for a marketing authorisation. Additional restrictions not available in the context of a MA such as an option to require a review of batch specific information by the authorities before release of each batch would be available to the authorities.

A EUA framework should also allow the **imposition of obligations** regarding quality, manufacturing and distribution, as well as the continuous monitoring of the benefit-risk profile of the product in terms of collection of efficacy and/or safety data.

Furthermore, if EUA was granted, the availability of the product (supply of the product in sufficient quantities) should be guaranteed by some mechanisms such as joint procurements.

### ***3.6. Conditional marketing authorisation***

#### **Problem statement**

- Currently, the concept of conditional marketing authorisation is linked with the demonstration of a 'Major Therapeutic Advantage' (MTA) of the concerned medicinal product vis-à-vis existing medicinal products. This criterion creates difficulties as it requires comparative data that is difficult to generate owing to the concomitance of developments, but also an incremental advantage in terms of safety or efficacy that might lead to dismiss new therapies in certain areas. For instance, in the field of oncology, whilst no gain in efficacy or safety are established vs existing medicinal products, alternatives can be of relevance for the patient that experienced failure with the existing therapies.

- Currently it is not possible to add to a standard MA, a new indication based on less comprehensive data (either in the context of conditional MA or MA under exceptional circumstances) which would require imposition of specific obligation(s) to confirm the positive B/R balance. This has been a limitation experienced for existing medicinal products, in particular for COVID-19 indications.
- Lastly, the PSUR cycle for a conditional MA is set systematically at a standard of 6 months (article 9 of Regulation (EC) No 507/2006). Having such systematic cycle is disconnected from the risk and need linked with the medicinal product. Acknowledging that there is an annual renewal, there is no benefit to have such systematic measure for the submission of PSUR. The system of EURD list introduced after the entry into force of Regulation (EC) No 507/2006 is adequate to manage the submission of data for a conditional MA without requiring derogative regimen – indeed the PSUR cycle through the EURD list can be adapted depending on the knowledge and risk associated with the medicinal product. Please refer also to concept paper 13 on pharmacovigilance.

### **Proposed solutions – in legislation**

- Explore removal of the criterion of Major Therapeutic Advantage imposing a comparison with existing medicinal products from the concept of CMA and to only refer to ‘unmet medical need’; this is supported by majority of committees members.
- Consider introducing a legal basis for the conditional authorisation status to be indication specific. By analogy the same should be introduced for an exceptional circumstances status linked to an indication.
- It is suggested to delete the *lex specialis* provision article 9 of Regulation (EC) No 507/2006 imposing a 6-monthly PSUR submission and apply instead the standard regimens *as per* the EURD list.

### **3.7. Marketing authorisation under Exceptional Circumstances**

#### **Problem statement**

- A MA under exceptional circumstances is granted subject to certain conditions, so called specific obligations (SOBs). Continuation of such a marketing authorisation shall be linked to the annual re-assessment of the conditions mentioned above. The SOB(s) may include an identified programme of studies to be conducted within a specified time period and aim at the provision of additional safety and efficacy data, e.g. a registry or an observational cohort study, where data is collected and reported annually based on an agreed protocol.  
The lifecycle management of these MA need some adaptations to be proportionate to the need and the risk instead of the current systematic approach that leads to substantial administrative burden without no public health value. Acknowledging that the MA dossier is likely to remain non-comprehensive and therefore particular scrutiny should be operated, the level of this scrutiny often evolves during the lifecycle of the medicinal product and might not justify anymore some specific obligations as no relevant additional data would be generated or no particular monitoring of the patients are needed. In addition, the annual cycle for re-assessment is too rigid and not adapted to the knowledge of the product. Indeed, relevant data might not be available on an annual basis which renders this procedure purely administrative without added value. For those cases, where the dossier is non-comprehensive (and therefore should remain under exceptional circumstances) but no specific obligations is needed anymore, it is proposed to not have *ad hoc* re-assessment but instead to rely on standard PSUR evaluation.



- Currently it is not possible to add to a standard MA, a new indication based on less comprehensive data (either in the context of conditional MA or MA under exceptional circumstances) which would require imposition of specific obligation(s) to confirm the positive B/R balance.

### **Proposed solutions – in legislation**

- Introduce flexibility in the cycle for re-assessments after a certain time (e.g. 2 years after the MA), proportionate to the knowledge on the product (including the risk, the need to monitor patients and the likely availability of new meaningful data).
- For those cases where the specific obligations are no longer necessary, consider not requiring a re-assessment anymore and use PSURs instead.
- Consider introducing a legal basis for the MA under exceptional circumstances status to be indication specific.

## **4. Options for more collaboration with international partners**

### **Problem statement**

- ***EU-M4all (article 58 procedure)***

The Article 58 procedure has demonstrated its ability to have real public health impact. However, the uptake of art 58 scientific opinions by pharmaceutical industry and other sponsors is disappointing (only 12 opinions in 17 years (2004 – 2021) so far resulted in 142 registrations).

The Agency has seen recent examples of disease areas where there is a need for medicines for both the EU and the non-EU population (e.g., Ebola, tuberculosis, dengue).

The possibility to apply for both EU-M4all (Article 58) and a European Union marketing authorisation at the same time has been introduced. However, this is considered a duplication of work for the Committees and double administrative burden for applicants, including double fee for the assessment and maintenance of licence in the post authorisation life cycle; while misperceptions by LMIC regulators and other stakeholders that there are double standards – one for medicines that are used in the EU and another for medicines recommended for use in LMICs, are not totally alleviated. Therefore, it would be beneficial to formalise and offer the possibility for manufacturers or sponsors to benefit from both Article 58 and the European Union marketing authorisation at the same time, as in one assessment with two opinions.

There is a need to also strengthen the benefits and incentives for Art 58 applications and to enhance the post-approval phase and monitoring.

- ***International Collaboration with non-EU Regulatory Authorities***

EMA could avail itself of an increasing cooperation with global regulators. With the OPEN Pilot, EMA aimed at reaping the harvest of its international cooperation while keeping full scientific and regulatory independence. Non-EU Regulatory Authorities currently have no role in the CHMP/CAT decision-making.

It might be valuable to envisage a possibility on a voluntary basis to share work for the assessment with international partners (FDA, Health Canada, MHRA, etc) to the extent the submitted data are

common in a way to (partially) rely on other assessment report or potentially allocate different parts of the assessment between the participating regions (similar to the concept of multi-National Assessment Teams at CHMP/CAT), when parallel applications and in case of shortness of resources. Issues may arise if the regulatory framework or policy are different from each other but would be useful in particular in emergency/rare conditions where experts are limited.

## **Proposed solutions – in legislation**

### ***EU-M4all (article 58 procedure)***

- Remove the word 'exclusively' from art. 58 to recognise that a medicinal product may come for approval under the centralised procedure and Art 58 as well and in parallel.
- Strengthen the benefits and incentives:
  - Fees regulation: Criteria of fee reductions not formalised and need to be granted on a case-by-case by the Director General, need to foresee a systematic fee reduction.
  - Develop under Art 58 similar incentives than the ones for orphan designation (e.g. fee reductions or access to research grants).
- According to Art 58 of Regulation (EC) No 726/2004 refers to Art 6 which lays down requirement for an application in accordance with Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC, which implies that applicants for EUM4all or their contact points must be established in the EEA. To avoid such limitation, it is proposed to add 'mutatis mutandis' to the reference to Article 6.

### ***International Collaboration with non-EU Regulatory Authorities***

- To reflect on the introduction of a legal basis to allow the possibility to rely on other assessment reports (partially or fully) from agencies with similar maturity levels and/or share work for the assessment with international partners (FDA, MHRA, Health Canada etc) i.e., multinational team not regularly but on ad-hoc basis for specific disease areas, or when parallel applications.

## **Proposed solutions – in guidance**

### ***EU-M4all (article 58 procedure)***

- Develop a pathway whereby manufacturer could benefit from both 'Article 58' advantages and EU Central pathway advantages while minimising duplication of work or fees with as in one assessment with two opinions or at least a work-sharing submission with reduced fees. There is no visibility for EMA on which national approvals are subsequently obtained by 'Article 58' products. Even where opinions are well accepted, the pace of national assessment is no quicker than with other SRA approvals.
- To consider guidance to facilitate downstream activities post-art.58 such as a new, collaborative review pathway (CRP) directly with National Regulatory Authorities (NRAs) outside the EU, ensuring a CRP post CHMP opinion phase with NRAs assessment/approvals within an abbreviated timeframe and allowing opportunities for post-approval communication with NRAs on
  - Safety concerns
  - Drug variations
  - Label updates

## ***International Collaboration with non-EU Regulatory Authorities***

In connection with the proposal for work sharing assessment with international partners (FDA, MHRA, etc), clear guidance would be needed to operate this tool e.g. describe in detail the conditions under which such collaboration with international partners can take place and/or build on the OPEN pilot phase.

## **5. Involvement of patients and HCPs**

### **Problem statement**

- The current legislation explicitly refers not just to “efficacy” and “safety” but to “benefits” and “risks”, requiring value judgment to be made on the estimated objective properties of candidate medicinal products. Such value judgments should ideally be gathered from a multitude of complementary sources, including inclusion of patient and HCP representatives and more systematic studies of patients’ preferences.
- However, there is no provision in the current legislation for civil society representatives (namely patients and healthcare professionals) to be full members within the CHMP and the HMPC as per current practice with a voting role and no rapporteurship role.
- Despite this, EMA has involved patients and healthcare professionals in their work (e.g. expert meetings, oral explanations, written contributions, collaboration with academia on patients’ preference studies etc). This input has been taken into account by the Committee in their decision making, however the fact that these interactions are not systematic leads to missed opportunities for these unique perspectives to be heard and considered.
- Formalising the participation of patients and healthcare professionals as members will ensure that the CHMP and HMPC have access to patients’ views and concerns. These perspectives represent a complimentary dataset that will contribute to CHMP/HMPC deliberations and ensure the resulting outcomes have duly taken into consideration the key perspectives from these stakeholders. This is also evidenced from experience over many years within the other committees.
- There is currently no provision within the current legislation to have healthcare professional representative members at the COMP. For the same reasons explained above, this should be considered during the legislative review.
- Currently there is an inconsistency in the number of representatives and alternates of civil society member for each committee.
- Regarding civil society membership of EMA Management Board, there is currently no provision for alternate members. Considering the workload and the fact that patient and healthcare professional representatives are not supported by any other means, having an alternate would aid their participation. In addition, the terminology ‘Representative of doctors organisations’ limits the scope of potential members.
- Civil society members of EMA’s scientific committees and management board (nominated by EC) are not remunerated for their work, nor their time invested at EMA. These members work on a voluntary basis, contribute a significant amount of time and effort, and their input is essential to optimal output of key EMA activities. In order to ensure participation of civil society, it is proposed that civil society members of EMA committees and management board be remunerated.
- The current legislation also foresees that the committees may establish contacts, on an advisory basis, with parties concerned with the use of medicines, in particular patients and healthcare

professionals. Input from these stakeholders is an integral part of EMA's regulatory process and is needed to obtain the best regulatory outcomes, however they are not remunerated for this work. Participating in EMA activities takes a considerable amount of time: meeting preparation, document review, considering committees questions and providing input, and also often requires finding cover or cancelling normal work and/or activities. Lack of financial support is an important element currently limiting access to the best available patient and healthcare professional representatives. It is proposed that patients and healthcare professionals be remunerated when they are involved and contribute to committee's activities .

- On a different note, regarding the PDCO composition, the Paediatric Regulation foresees that CHMP appoints 5 of its members and alternates to PDCO, i.e., that 5 CHMP members/alternates are at the same time also member/alternate in PDCO. In practice it has proven difficult for CHMP to appoint 5 members in the joint membership positions to. Currently, there are only 3 positions filled and out of these, 1 had recently decided to discontinue the joint membership.

CAT is the other committee with a joint CHMP membership but with difference in the legal provision i.e. for PDCO both the CHMP member and alternate take up membership in PDCO, for CAT, only the CHMP member becomes member in CAT who can then nominate his/her own alternate for CAT (with CHMP agreement). For CAT, this has worked without major problems: for the moment the 5 joint positions are filled but with flexibility that two (of the 5) CHMP members are (almost) never attending the CAT meeting, and their role in CAT taken up fully by the alternate members.

As it is difficult for CHMP to fulfil the legal requirement in particular for PDCO while this joint membership has been found very useful for the CAT, specifically, to voice and refer back information/position between CHMP/CAT, it should therefore be considered to review this legal requirement for PDCO and CAT to facilitate such joint membership and/or to give opportunity to member states to appoint members directly.

## **Proposed solutions – in legislation**

- Update the relevant legislation to incorporate civil society representatives as members of CHMP and HMPC to bring it into line with the composition of other committees (COMP, PDCO, PRAC, CAT) and allow systematic inclusion of their perspectives, where appropriate.
- Update the relevant legislation to include healthcare professionals as members of COMP.
- In light of the inconsistency in the number of members of each committee, consider updating the relevant legislation to take a holistic approach in the number of representatives/alternates of civil society members for each committee, e.g., 2 members and 2 alternates per committee.
- Update the relevant legislation to include provision for civil society alternate members and update the terminology from 'doctors organisations' to 'healthcare professional organisations' to align to the broader scope of this stakeholder group.
- Exploring possibilities allowing civil society members of EMA's scientific committees and Management Board to be remunerated, and also for remuneration of patients and healthcare professionals when providing input/advice to committees.
- Update the PDCO and CAT composition regarding the CHMP joint nomination that CHMP may appoint up to 5 of its members or co-opted members from five Member States, with alternates either proposed by their respective Member State or, in the case of co-opted members, identified by the latter on the advice of the corresponding co-opted member.

## **Proposed solutions – in guidance**

- Role of the civil society representatives as members of CHMP should be clarified in guidance as already the case, they are expected to have a voting role but no rapporteurship role.
- While the contribution of patient representatives can be useful, it is important that conditions are defined. Background, skills and knowledge of such a representative could be described in a profile.

## **6. Public hearings at CHMP**

### **Problem statement**

- There is no provision in the current legislation for the CHMP to hold public hearings.
- Although limited experience and analysis acquired through public hearings held at the PRAC has demonstrated that they add value by collecting views from all the civil society, enrich the assessment and foster trust in the system.
- Public hearings have been instrumental in providing insights and information to PRAC on the different views and positions of the various stakeholders and this input contributed tangibly to the assessment and final recommendations of the specific medicine(s) under review.
- Public hearings would equally provide a valuable tool for the CHMP to listen to, to gather the views and experiences of the public, and relevant stakeholders in a transparent way, on specific medicines evaluations such as referrals, as and when needed; it also has the potential to promote trust in regulatory decision-making. As for public hearings at the PRAC, this might be of benefit in particular in the review of authorised medicinal products (e.g., in the context of referral procedures).

### **Proposed solutions – in legislation**

- Update the relevant legislation to allow the CHMP to convene public hearings when they consider this would bring added value to an ongoing assessment and when justified by the interest of the public.

### **Proposed solutions – in guidance**

There will be a need for clear rules on how and when public hearings would be convened.

## **7. Raw data format**

### **Problem statement**

Currently, the 2001/83/EC directive and its Annex I only refer to the '*documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials*'. However, data is not mentioned whilst in the data value chain, information is generated from data.

In contrast, raw data is only explicitly stated in the EU Regulation No 536/2014 on clinical trials on medicinal products for human use. It states that for '*cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidance for the formatting and sharing of those data*'.

Furthermore, individual patient data listings appears the only format by which assessors can have access to raw data as per the ICH M4E(R2) on Common technical document for the registration of

pharmaceuticals for human use – Efficacy whereby reference is made to *'Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study'*.

Therefore, there is a lack of alignment in current legislation in terms of terminology for data and data format. Besides, current legislation is not up to date with recent progress on information access and exchange whilst at the same time there is a trend for the increase of documents' structuring and enabling of electronic data exchange.

### **Proposed solutions – in legislation**

- Proposal to align data terminology in current legislation to be format agnostic and allow more flexibility about information/documentation exchange between applicants and EMA for certain initial marketing authorisation application and other relevant post-authorisation regulatory procedures.
  - The request for applicant to submit information needed for assessment should be irrespective of the format and how information is shared.
  - Legislation usually does not go into technical details; reference to 'summaries and results' should be replaced with wording agnostic to data format or preferably the term 'data' can be added.
  - The same principles should apply to non-clinical and manufacturing data.

### **Proposed solutions – in guidance**

- Guidance, including technical guidelines, need to be produced by EMA to clarify how raw data should be presented (e.g., static pdf listings or electronic structured data), in what data format and for which type of applications, in complement to other required studies and results. It should also clarify the requirements to be checked at validation by EMA.
- If an agnostic terminology is used, guidance to clarify data format submission (e.g., summaries, study report) will be needed which can be through NTA (vol 2B – CTD).

## **8. Implementation of the ICH Q12 Guideline on Lifecycle Management and future Quality / Multidisciplinary Guidelines**

### **Problem statement**

The current definition of a 'variation' in REG (EC) No 1234/2008 under Article 1 is "*any amendment to ... the information referred to... in Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto..*" refers to the directive and its annex as regards to the quality documentation.

In particular, to support the full implementation of the ICH Q12 Guideline on Lifecycle Management, the ability to differentiate between Established Conditions (information subject to variation if changed) and Supportive Information (not subject to variation if changed) within Module 3 dossier sections needs to be foreseen in EU legislation.

The CTD Module 3 includes different types of information; both forward looking legal obligations ('how a medicinal product will be manufactured and controlled') and historic supporting information (including pharmaceutical development, validation and stability data). These data require different

lifecycle management; legal obligations may be revised, whereas supportive (historic) data will not change. Additional/new supportive data can, however, be submitted to support changes to legal obligations (e.g., additional stability data to support a change the approved shelf life).

As currently written, any change to Module 3 content referred to in Annex I of 2001/83/EC triggers a variation.

(For reference please see [‘Note on EU implementation of ICH Q12 \(guideline on technical and regulatory considerations for pharmaceutical product lifecycle management\)’](#))

The quality part of current Annex I (CTD content) is directly copied from ICH M4(Q) guideline. When this ICH guideline will be updated in the future (revision has just started), it cannot be implemented in EU without updating the current Annex I of the Directive.

The revision of the variation framework should be closely aligned with the parallel flagship initiative on regulatory efficiency in the Pharma Strategy: “Propose to revise the variation framework for medicines, through changes in legislation and guidelines, to make the lifecycle management of medicines more efficient and adapted to digitalisation – 2021-2023” to keep path with the regulatory science progress and to aim at reducing the administrative burden as much as possible in the EU regulatory system including but not exclusively through digitalisation, reduction of number of variations and reduction of variations requiring an adoption by CHMP.

## **Proposed solutions – in legislation**

- There is an urgent need to re-open the variation regulation and guideline to allow for quick efficiency gain as the current framework for managing post-authorisation procedures has a massive impact on the capacity of the network, in particular as some processes have become increasingly complex from an administrative perspective, hence review of the variation system should allow for simplification and avoidance of unnecessary administrative complexity e.g. through digitalisation, reduction of number of variations and reduction of variations requiring an adoption by CHMP and an enhanced role of EMA in the assessment of quality variations (cf section 11 as well).
- The ICH 12 concept of Established Conditions / Supportive Information should be introduced into EU legislation and guidance, i.e., a clear differentiation of the CTD Module 3 content between legally binding information required for MA and supporting (historical) data. Legally binding information would be subject to variations/approval if changed, supporting (historical) data would not. Following from this, I definition of a ‘variation’ can be reconsidered, at least in respect to quality variations.
- It should be carefully considered how Annex I of the Directive (or similar future legislation) will interface with other legislation and guidelines, e.g., Variations Regulation, Eudralex Vol2B, ICH Quality/Multidisciplinary guidelines etc. so we will have flexibility to implement novel ICH scientific guidelines into EU regulatory system in a timely manner.
- Remove the CTD content from Annex I and refer instead to the NtA Vol2B which also defines the CTD dossier content. When the CTD structure will change in the future, it will be easier to update in EU at level of NtA guidance than in legislation. (preferred option)

## 9. Handling of multiple Marketing Authorisations

### Problem statement

Article 82(1) of Regulation (EC) No 726/2004

1. Only one authorisation may be granted to an applicant for a specific medicinal product. However, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons.

The EC has drafted and published a [Commission Notice on the Handling of duplicate marketing authorisation applications of pharmaceutical products under Article 82\(1\) of Regulation \(EC\) No 726/2004](#) which clarifies the applications falling within and outside the scope of Article 82(1) and provide guidance on the elements to provide/meet in order to seek the Commission's authorisation to submit a duplicate marketing authorisation application.

No pre-authorisation regimen for medicinal products submitted via purely national, MRP or DCP procedures which creates a differential treatment between marketing authorisations and operators depending on the route of authorisation.

It is questioned whether this *a priori* control is effective in ensuring free and undistorted competition. To EMA's knowledge, no evidence has been provided of anticompetitive behaviour.

In addition, this regimen does not cover post-authorisation phase which is therefore not regulated (e.g., no explicit requirement for an applicant to seek prior agreement from the European Commission before acquiring a second marketing authorisation for the same medicinal product).

Furthermore, the *a priori* administrative control leads to additional steps in the procedure that create additional complexity and risks of delaying procedures.

Taken into consideration the above, added value from this measure has not been established.

### Proposed solutions – in legislation

Proposal to align the regimens between centralised and national medicinal products. Further to an impact assessment as appropriate, the European Commission could consider deleting Article 82(1) from Regulation (EC) No 726/2004.

### Proposed solutions – in guidance

If the Article 82(1) of Reg 726/2004 were removed, it is understood that the Commission Notice on Handling of duplicate marketing authorisation applications of pharmaceutical products under Article 82(1) of Regulation (EC) No 726/2004 would be removed consequently.



## **10. Improvement - initial MAA process**

### **Problem statement**

#### **1. Increasing predictability of submissions to optimise allocation of resources**

The unprecedented workload related to the COVID-19 pandemic has revealed the resources issues in the network to the point that challenges are routinely experienced in allocating Rapporteurship that sometimes translated into delays.

Whilst this issue is multifactorial, it is essential based on the experience acquired by the authorities on the processing of regulatory procedures to optimise them in order to allocate efficiently the resources of the network to those activities that ensure a safe and effective use of the medicinal products.

Furthermore, there is no visibility of the development plans for products, especially if the applicant does not go for scientific advice. This puts us at a disadvantage vs other regulator.

An important element to optimise the allocation of resources is to increase the predictability of submissions by stakeholders. Indeed, the change of submission dates by the Applicants, sometimes at short notice, have a significant impact on the network capacity that has to block some assessment capacity for applications that are not submitted in due time. Acknowledging the differences with NAPs, a concept of timeslots for the centralised procedure should be considered. This could be built on the current letter of intent that provides indicative information on the date of submission and triggers downstream activities such as nomination of Rapporteurs. Such letter of intent could be reflected in the legislation to formalise it and could be operated with a contractual approach with regards to the change of the declared date of submission by the applicant, i.e., to be agreed by the authorities. In case of disagreement on the amended date, the authorities could have the possibility to deprioritise the application. This would allow better predictability and therefore optimise network capacity to evaluate dossier. This may also foster applicants to provide more precise date of submission and share in advance with the authorities any change of submission plan.

#### **2. Clarifying conditions that can be imposed for the safe and/or effective use of the medicinal product**

- Quality and non-clinical

In some cases, whilst the quality, safety, efficacy is established and the benefit-risk balance is favourable leading the CHMP/CAT to recommend the grant of a marketing authorisation, some elements on efficacy and/or safety needs to be further characterised. This leads to the possibility when duly justified to impose post-authorisation safety or efficacy studies when key for the benefit-risk balance (and in accordance with Commission Delegated Regulation (EU) No 357/2014 for PAES).

In rare occasions, it may be needed to impose studies on quality or non-clinical aspects – this possibility should be explicitly recognised in the legislation.

- Development beyond the terms of the MA

Furthermore, the specific case of improvements to the medicinal product beyond the terms of the MA should be considered. This is essential for dosing optimisation where the proposed dose scheme, whilst acceptable and justifying a positive benefit-risk balance, could be optimised (e.g. by lower the dose to decrease ADR occurrence without jeopardising the efficacy). As these developments are not strictly

within the terms of the MA and as it is not possible to impose developments beyond the terms of a MA, they lead to recommendations to the applicant to consider. Indeed, inclusion of obligations would not be effective as regulatory actions could not be taken in case of non-compliance outside the terms of the MA. Linked with the reflections on gradual response in case of non-compliance and in view of optimising the safe and effective use of medicinal products, it is recommended to explore if such developments could be imposed with potential actions in case of non-compliance.

### **3. Increasing the range of responses to non-compliance situations**

Regulatory actions can be taken in case of non-compliance with the terms of the MA. However, the range of actions is limited, namely to restrict or suspend the use. In addition to regulatory actions, penalties are difficult to apply.

It should be considered if additional mechanisms, not necessarily connected with restrictions to the use of the medicinal product would be appropriate to allow a proportionate response to the extent of the non-compliance, but also take some actions in response to a non-compliance although there is no scientific/public health reason to restrict the use of the MA.

To this effect, it could be considered to have the possibility to take measures to reduce the period of data and market protection.

### **Proposed solutions – in legislation**

- Introduce reference to the letter of intent in the legislation and use this concept as a 'contractual-like' tool to ensure better planning of MAA submissions from the applicant and better adherence by applicant's to their initial planning with possibility in case of breach of the agreed date of submission to delay the submission for a product not fulfilling an unmet medical need. This could translate in the legislation by mandating the applicant to notify their intent to submit no later than 4 months in advance. In case of non-compliance the applicant should re-submit a new letter of intent with a new date no later than 4 months, unless an earlier date is agreed with the EMA.
- Clarify that quality or non-clinical studies could be imposed and explore whether it could be possible to impose development improvement beyond the terms of the MA to increase the safe and effective use of the medicinal product (e.g., dosing improvement). This could be achieved by the addition in article 9(4) of Regulation (EC) No 726/2004 (and equivalent in Directive 2001/83/EC) of '(cd) if appropriate, details of any recommended obligation to conduct other post-authorisation studies.'
- Proposal to have measures to allow proportionate and gradual actions in case of non-compliance with the terms of the MA, such as the reduction of data/market protection period.
- Include the grounds for suspension or revocation of a marketing authorisation in the Regulation (EC) No 726/2004 as well.

### **Proposed solutions – in guidance**

- Strengthen the need for Industry to provide better up-front planning for submission of initials and submission of responses to LOQs/LOIs (linked to planning of network resources) (links to the 'slots' NCAs give connected to registration fees and/or as needed, change of rapporteurship)
- Aim at having earlier touch points with companies and committees for initial MAA and also significant variations to streamline assessment (earlier than D80 concept for iMAA): revisit timetables and approach to questions. Reduce CHMP/CAT LoQ to essentials (i.e. impacting B/R), allow Rapporteurs to interact directly with applicants, outside of formal clock-stops, in order to

clarify minor points and present issues encountered earlier than planned milestones to the Committee for discussion/steer

- More systematic use of SAG/AHEG when committees are split (not waiting for re-examination).
- Simplify Rapporteur and CHMP/CAT overview / assessment report (i.e., EPAR) and introduce clearer guidance for non-clinical and clinical overviews that they become more uniform and relevant for the assessment.
- Re-think Rapp and Co-Rapp role; use two independent assessments only for key procedures like first in class, new mechanism of action, etc.
- Re-examination procedure to be simplified / better explained.

## **11. Process improvement – post-authorisation procedures (only affecting Directive 2001/83/EC or Regulation (EC) No 726/2004)**

### **Problem statement**

1. The current framework for post-authorisation changes to marketing authorisations is generating a high level of workload for all stakeholders (for instance, in excess of 80% of the workload of the EMA therapeutic offices is related to Type II variations).
2. In practice, non-urgent labelling updates approved via variations or notifications are often implemented in product packaging twice a year and in compendia once a year; there is therefore somewhat of a disconnect between the system of multiple, complicated and overlapping label updates and their implementation to the medicines that reach the patients.
3. Under the current framework except in the context of USR and referral, there is inability of the regulators to mandate changes to labelling.
4. Reviewing the added value of specific procedures, e.g., sunset clause, renewals or transfers of a marketing authorisation, versus the administrative burden that they generate.
  - 4.1. The 5-year renewal procedure creates duplication with the obligations to provide PSUR, the obligation to submit forthwith any new data that might impact the benefit-risk balance, the obligation to submit variations to keep the dossier up to date with the state-of-the-art, as well as the data mining through the signal management procedure. It is therefore, in line with concept paper 1 on MR/DCP and concept paper 13 on pharmacovigilance to delete 5-year renewal procedure.
  - 4.2. The sunset clause was created in order to facilitate the lifecycle of MA, avoiding existence of MA that do not lead to marketing of the medicinal product in the EU. This provision has led to the creation of a monitoring system, management of exemptions (e.g., where the MA is used as reference for non-EU countries) that is complex to operate, resource-demanding for the stakeholders for an added value that is limited. It should be considered whether there is some benefit to maintain this provision.
  - 4.3. The Transfer of a marketing authorisation Regulation (EC) No 2141/96 would benefit from being reviewed to optimise the transfer process and introduce technical updates. This is less urgent than the review of the variation regulation.

## **Proposed solutions – in legislation**

- Reviewing the variation Regulation (EC) No 1234/2008
- Abolish 5-year renewals duplication with other means that ensure the continuous monitoring of B/R)
- Reflect on possibility for the regulators to change unilaterally the product information, mandating changes that MAHs must abide by.
- Give power to the PRAC to adopt opinions on certain post-authorisation procedures incl. PSUR, variations without the need for CHMP/CAT to adopt as well (please see also concept paper 13 on pharmacovigilance, section 21. Action: Reducing 'the duplication of work 'between EMA Committees').
- Consider a parallel revision to the variation legislation, to simplify and streamline, adopting e.g., annual updates in lieu of many types of variation and limiting variations to changes that impact the B/R.
- Abolish sunset clause (as for veterinary Regulation).
- Update transfer of a marketing authorisation legislation.
- Streamline Commission Decision phase, in particular for medicinal products fulfilling an unmet medical need or authorised in response to an emergency situation.

## 12. Concept paper for EC on **Product Information**

**Main theme:** Simplification and streamlining, especially with regard to Title V of Directive 2001/83/EC

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic leads	Experts from EMA, HMA/CMDh
Drafting group	Experts from QRD, CHMP and EMA, HMA/CMDh

### December (mature interim paper - final paper two months later)

#### *Questions to be considered (not exhaustive list, taken from EC document)*

- 1. Better recognition of multilingual packs, learnings from flexibilities used during the pandemic*
- 2. Reduction in legislative and national requirements for packaging*
- 3. Facilitating ePI or more flexibility on multilingual packs, or EN-only derogations for hospital only vials*
- 4. Strengthen use of standards (e.g. ISO formats, e.g. for numbering)*
- 5. Omit need for MAH in name from legislation*
- 6. Remove requirement to place a special warning that the medicinal product must be stored out of the reach and sight of children for products administered in hospitals only*
- 7. Marketing authorisations without national translations (from CP1)*
- 8. Remove need to have the same name for all MS for generics of CAPs (from CP2)*

## **Recommendations for change**

The questions above as requested by the Commission have been considered in this document, and several further points have been added. Considering that there remains uncertainty around the speed at which electronic product information innovations can be adopted and incorporated into national

systems, this document discusses both the paper based solutions which are more applicable in the short term, and electronic solutions which may, in the medium or long term, resolve some remaining issues. Such approaches have been raised here for consideration in legislation and guidance updates as appropriate. The background and proposals are as follows:

## 1. Facilitating multilingual packaging

The European Pharmaceutical market permits the use of multilingual text for labelling particulars for at least one component of the pack for a medicinal product, e.g. immediate and/or outer packaging, and/or package leaflet, or for all components. As multilingual packaging allows for the distribution of medicines in multiple Member States (MSs), measures to facilitate multilingual packaging can unite the European Pharmaceutical market and help resolve problems in respect of availability of medicines. Considering the balance afforded by the requirement in Article 56 that these particulars should remain easily legible, clearly comprehensible and indelible, it is considered that MSs could explore further ways of facilitating multilingual packaging as outlined in each section below.

The recommendations below 1.1, 1.2, 1.3 and 1.4 relate to all marketing authorisation procedures, e.g. NAPs and CAPs, unless further specified (e.g. 1.4.3). The proposed updates to the legislation outlined in this document are summarised in Annex 1.

*(Note: for the purposes of this concept paper, 'multilingual packaging' refers to the concept of allowing several languages on a pack. The term 'pack' is the general term for the physical package which may include inner and outer packaging as stated in Title V of the Directive). This discussion also incorporates 'multinational packs' where the same language(s) is/are shared between two or more MSs, where special attention should be paid to the particularities of the same language in different countries.)*

### 1.1. Allowing further exemptions for multilingual packaging

Multilingual packaging is currently permitted under Article 63.1 of the Directive, and it is not intended in these proposals to limit the use of the current provisions. However by defining a further scope for labelling exemptions, e.g. for 'hospital only products' or 'healthcare professionals administered products' and in cases of 'space constraints on the printed labelling', packs may be shared across markets due to improved alignment of expectations, and as such assure availability in small markets. More flexibility could be afforded on exemptions from Title V expectations for products administered by healthcare professionals, e.g. parenteral products, and for products where a multilingual pack is envisaged, not just in the case of severe availability issues arising or for 'hospital only' products as currently outlined in Article 63.3. This would also help orphan products or paediatric products requesting multilingual packs or specific labelling exemptions due to their small sales volume.

The proposals for legislation and guidance are outlined below:

#### Proposed solutions – in legislation

An expanded scope for '**labelling exemptions**' to facilitate multilingual packaging can be achieved by a multifaceted approach to expanding the current Art 63.3, as outlined in points below.

Article 63.3 currently reads: *Where the medicinal product is **not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability** of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the*

*obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

Firstly, it is proposed to include 'healthcare professional administered products', 'hospital only products' and 'space constraints' in legislation (defined as necessary) within Art 63 provisions, and link any relevant exemptions to this inclusion, e.g. application of minimum particulars on labelling, or permission to use multiple package leaflets, provision of package leaflet in EN only, or use of electronic product information (through mobile scanning technologies on the carton) or other electronic access to the relevant and current version of the package leaflet. Such 'hospital only' products or 'healthcare professional administered products' (defined in a manner suitable for use in data systems such as SPOR) should also encompass situations where some medicines predominantly administered by healthcare professionals may occasionally be dispensed for self-administration by suitably trained patients (or ambulatory use), to allow such exemptions to be retained where appropriate.

An approach to clarify that Art 63.3 covers situations where severe problems in respect of availability are foreseen will also be useful to cover situations where multilingual packaging is used to improve availability. Similarly, a clear reference to situations of 'space constraints' arising on the printed materials, due to proposed multilingual packaging or to the small size of the pack for which a labelling exemption could be granted, is needed. Space constraints on the printed materials are not reflected in the current legislation and only indirectly considered for the immediate label (i.e. Art 55.2 for blister packs and Art 55.3 for 'small immediate packaging units'), thus currently lacking a clear definition in European legislation and lacking a harmonised definition in national legislation, even for monolingual packs. This could be solved by revising Art 63 accordingly, providing an adequate and clear legal basis for solving space constraints via omission of particulars for all types and sizes of packs.

Such an expanded scope to allow **labelling exemptions** where there are multilingual packs proposed, including those dispensed to patients for self-administration, will be helpful in this regard, and the details could be elaborated in associated guidance (see 1.1 proposed solutions - guidance). Expanding the scope of Article 63.3 could also allow multilingual outer packs to be exempted from the full requirements for outer pack as currently outlined in Title V. It also provides a solution for monolingual containers, such as single unit eye drops, where even minimum particulars according to Article 55 cannot be displayed. It is acknowledged that minimum particulars may not be appropriate for example for OTC products, hence the proposed approach to link to additional guidance to address such nuances.

Changes to the legislation to facilitate 'labelling exemptions' are discussed below, while 'language exemptions' as currently stated in Article 63.3 are discussed further in Section 3 of this paper.

It is considered that Art 63.3 relating to **labelling exemptions** could be further expanded as follows, (see Annex 1 for a combined overview of legislative changes proposed):

*3. Where the medicinal product is not intended to be delivered directly to the patient, i.e. hospital only products, healthcare professional administered products, medicinal products intended to be used in the context of pandemics/health emergency situations, or where there are severe problems foreseen in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.*

*4. Where space constraints are foreseen on the printed labelling and package leaflet materials of the medicinal product due to the small size of the pack/container/label or due to the necessity of displaying the same information several times in different languages to facilitate multilingual packaging, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.*

In summary, this approach would allow labelling exemptions where required for orphan medicines, advanced therapy medicinal products (ATMPs), 'hospital only products', 'healthcare professional administered products', severe availability problems (e.g. small markets), and also exemptions due to space constraints for multilingual and monolingual packs, as such an approach may be preferable to language exemptions. A concurrent update to Article 65 to include preparation of guidance on 'harmonised provisions for the implementation of Article 63' is therefore proposed.

Further actions are also proposed to facilitate multilingual packaging as follows, e.g. in cases where full particulars cannot be displayed:

**Amending Art 58** to allow provision of (full) information through mobile scanning technologies could facilitate multilingual packaging: *The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is ~~directly~~ conveyed on the outer packaging or on the immediate packaging.* This could also be expanded to include *'[...] packaging, or conveyed by other means as agreed by Member States where the medicinal product is placed on the market'* to facilitate electronic information as outlined in Section 2.3 below.

A similar change analogous to the veterinary regulation 2019/6 Article 14(3) could also be made to facilitate multilingual packaging, i.e. *The package leaflet shall be written and designed to be readable, clear and understandable, in terms that are comprehensible to the general public. Member States may decide that it shall be made available on paper or **electronically**, or both.* This detail could be added to Article 58.

Allow a **shortened printed package leaflet**, limiting Directive requirements to critical issues only (potentially in conjunction with provision of full version in electronic format), would be helpful regarding space constraints in multilingual packs where a multilingual pack may not otherwise be achieved. This would also allow patients to easily focus on the most critical information and potentially improve comprehension, although concerns have been raised by some MS around the impact on incomplete information, understandability, transparency and safety. It should be noted that to date, a shortened package leaflet has not been accepted for CAPs, not even for the COVID-19 vaccines and therapeutics, due to the lack of a common definition of "key information" or agreement regarding the question of which sections of the package leaflet (as defined in Art 59) could be shortened or even omitted from the printed package leaflet without posing a risk to patients due to incomplete information. It is also noted in discussions on this topic, that a majority of QRD members are currently not in favour of shortened package leaflets due to lack of evidence of their suitability, however it is acknowledged that this proposal is somewhat linked to future work on a 'key information' section in the package leaflet which EMA is due to work on as part of the action plan arising from the Commission's report on shortcomings in the summary of product characteristics and the package leaflet from 2017. Therefore, this proposal is raised now for awareness only, to allow for any associated future planning in legislation.

The impact of **Article 59(g)** regarding **listing names** at end of package leaflet for MRPs/DCPs *'where the medicinal product is authorised in accordance with Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State'*, which in turn increases the length of the package leaflet, should be reviewed in a suitable forum, and potentially reconsidered as to whether it has been of benefit to patients in Europe. A proposal to delete this provision has been pre-emptively included in Annex 1 pending such further review.

## **Proposed solutions – in guidance**

Marketing Authorisation Holders (MAHs) could be recommended, in labelling guidance and during scientific advice request, to consider use of **innovative labelling** in order to display full/reduced/minimum multilingual information on small immediate container, e.g. wrap labelling and



potentially codes with encrypted electronic information when relevant. While it is considered premature to outline these options in legislation, it is noted that such options are used in other product classes, and technology-based solutions may be linked to discussions on electronic product information Section 3 below. Such approaches may reduce requests for labelling exemptions. However where labelling exemptions are needed, the following could be applied:

The **exemptions** according to an expanded Art 63.3 for 'hospital only products', 'healthcare professional administered products' and 'space constraints', and as described below, could be further outlined in guidance in accordance with Art 65 on the expectations around the implementation of Art 63, e.g. provision of printed package leaflet in EN only, use of electronically displayed package leaflet only instead of paper package leaflets (through mobile scanning technologies), common definitions of such products, or what minimum particulars are required on the outer pack. This would be helpful to coordinate the approach across MSs, and expectations around what appears in the printed materials and in the PI annexes for CAPs. For example, it could be permitted for 'hospital only products' or 'healthcare professional administered products', whilst retaining any necessary special warnings for the specific product, to:

- remove the requirement to place the warning 'Read the package leaflet before use' on the pack;
- if the product contains excipients known to have a recognised action or effect, keep the reference to the excipient but remove the warning – "See package leaflet for further information";
- alternatively, one overarching statement 'Read the package leaflet before use' could be considered to replace the separate similar statements for excipients, method of administration details, shelf life of the reconstituted medicine, or for full OTC dose recommendations in the case of non-prescription medicinal product as below;
- a review could be undertaken, whether for injectables, topical products or eye preparations as outlined in Art 54(d) excipients which do not have action or effect need to be listed on the packaging. A proposal to delete this requirement has been pre-emptively included in Annex 1;
- remove <This medicine is authorised in the Member States of the European Economic Area <and in the United Kingdom (Northern Ireland)> under the following names:>, as it is considered that this is unlikely to be of use for hospital products (and indeed Art 59(g) could be reconsidered in general as to whether it is useful or not - see under 1.1 legislation above)

For non-prescription medicines exemptions from full labelling are already exceptionally accepted on a case-by-case basis. The immediate labelling is for many non-prescription products very important as the outer package is easily discarded. A short form of indication and dosage can be accepted on inner labels for non-prescription medicines as outlined in the QRD template. Such flexibility needs to be maintained in guidance for non-prescription products.

At present a 10 mL **container capacity limit** is applied in the QRD templates, above which full particulars according to Art 54 are expected on the immediate labelling. Limits are separately stated in the national legislation of some MSs (for example different capacity limits of 10 mL or 20 mL are currently applied). No capacity limit is currently applied in the CMDh multilingual packaging pilot applicable to all MSs, as minimum particulars can be requested in all cases where multilingual packs are proposed. The existing 10 mL limit is problematic where a multilingual container is proposed, as space decreases proportionately depending on the number of languages applied. It is therefore proposed to revise the guidance regarding minimum particulars for immediate packaging. A multifaceted approach is proposed based on container size and space constraints:

A definition regarding the **size of immediate packaging units** for which minimum particulars are generally accepted could be considered in guidance to ensure a harmonised definition of this provision across all MSs. In line with the recent change in the *veterinary*, for example, a capacity of 50 mL could

be considered for monolingual packs. Such an approach to expand the current limit, defined in guidance rather than legislation, would allow the use of minimum particulars for containers up to a volume of 50 mL in all MSs, without the need for requesting an exemption. A labelling exemption according to the revised Art 63, based on **'space constraints'**, could then be requested in case of containers exceeding a volume of 50 mL, if needed. This would avoid difficulties with monolingual packs, as experience has shown that it can be difficult to include full particulars even in 50 mL packs. **Amending Art 63** to allow such labelling exemptions due to 'space constraints' to be requested without any restrictions (i.e. independent of the pack/container size and the number of languages used) would further facilitate the preparation of multilingual packs, by providing a legal basis for such an approach. It is noted that maximum container volume is naturally constrained by manufacturing quality considerations, e.g. intended fill volume and stability, and font size is mandated in the Commission Readability guideline, therefore a proliferation of languages is unlikely. For multilingual outer packs a level of detail between that of full text (Art 54) and minimum particulars (Art 55) could be permitted during assessment, for example on the understanding that special warnings are retained as appropriate. This would be facilitated by the proposed changes to Art 63.3.

Pros and cons of this approach to amending Art 63 and capacity definitions have been identified, such as leading to minimum particulars even on large packs, and that such a multiplicity of languages may also decrease the legibility and comprehension by the patient (Art 56). Guidance on Art 63 should outline that also for MRPs/DCPs multilingual mock ups of labelling, with repeated information in English in the proposed labelling, should be submitted early in the procedure, preferably with the Application, to facilitate the assessment of whether a multilingual pack is feasible or labelling or language exemptions will be required.

To conclude, removing or increasing the limit for capacity restrictions, and clearly facilitating situations of space constraints, could help increase availability of medicines due to the improved possibility for preparation of multilingual packs and small containers.

The MRP/DCP pilot on multilingual packaging (as outlined in the CMDh BPG on Multilingual Packaging) is currently ongoing, whereby a EU full/reduced harmonised text template can be agreed during the procedure whilst retaining key safety information on the outer pack. The agreed text reductions can then be applied in any future multilingual packs, e.g. a 'dual labelling approach', while retaining full text on monolingual packs. This approach allows flexibility for MAHs and MSs to quickly prepare future multilingual packs based on reduced text. This approach is not considered helpful for CAPs to facilitate multilingual packs due to the need to maintain one set of labelling for CAPs. As the use of multilingual packs is routine for CAPs (i.e. a multilingual pack – the trilingual BE pack that could be marketed in up to 6 MS - is needed for every CAP, and further languages may be accommodated where readability is retained), respective procedures regarding mock-up review and optimisation have been in place for decades. The QRD group is currently working on respective guidance to further improve current practice, especially regarding transparency. Notwithstanding the two co-existing approaches above, the preference is to agree **some common exemptions** applicable to all packs, and therefore alignment of exemptions through guidance is preferable.

The concept of a **shortened printed package leaflet**, for example for multilingual packs, would need to be explored further to define and balance the needs for clearly comprehensible, transparent, relevant and accurate information which do not reduce safety and compliance.

## ***1.2. Reduction in legislative and national requirements for packaging***

The following subsections highlight areas where reductions in legislative and national requirements will facilitate multilingual packaging for both CAPs and NAPs. Such amendments (for example those

proposed in guidance below) will also be useful to facilitate removal of superfluous information on monolingual packs.

### **1.2.1. Common approaches to reduce EU requirements**

Proposals are outlined below to revisit the particulars to appear in the package leaflet, and outer and immediate packaging applicable to all medicinal products to ensure information is succinct and avoid unnecessary repetition.

Extend the flexibility to apply minimum particulars for small immediate packaging to the immediate packaging of all medicinal products where appropriate.

#### **Proposed solutions – in legislation**

Revisit the corresponding articles of the legislation: amend Article 55 to allow extension of minimum particulars to all immediate packaging. Minimum particulars for all capacities could be achieved by repealing Art 55.1 and amending Art 55.3, meaning, for example: "*The following particulars at least shall appear on immediate packaging units, other than those referred to in paragraph 2, on which the particulars laid down in Articles 54 and 62 cannot be displayed: (...)*"

It is noted that a further level of information may be required for immediate packaging for OTC products which are not in the form of blisters, or in some cases special warnings or key technical information may be need to be retained on an immediate package. However it is preferred not to include this as an additional point to Art 55, but handle through relevant guidance and existing QRD templates based on the assessment of the outer packs.

#### **Proposed solutions – in guidance**

Revisit the QRD templates, appendices and national requirements periodically, for example to simplify standard statements as used in the Appendices for CAPs, or review QRD stylistic matters.

Allow routine exemptions which would be outlined in guidance, to facilitate agreement of text of multilingual packaging, analogous to MRP/DCP pilot and as already applied for OTC products in the QRD template which allows short form of indication, condensed form of dosage and warnings on outer packaging.

A further area where changes in guidance may facilitate multilingual packs is the review of the application of the requirements of Articles 54 and 55 of the Directive regarding inclusion of the method and route of administration to avoid superfluous information. The QRD guidance around Articles 54 and 55 relating to route and method of administration could be reviewed to avoid an interpretation that the route of administration should always be present (contrary to legislation). This interpretation currently leads to huge number of products with the route of administration written in every language, taking up valuable space. For parenteral products (and eye/ear/nose preparations), information about the route of administration is necessary (e.g. SC, IV, IM), however this is not the case for most non-parenteral products, (e.g. for tablets and capsules if the route of administration is "Oral use"). This clarification would also be helpful for monolingual packs.

Permit 'minimum particulars' (name, strength, INN, exp, lot, MAH, and method of administration if necessary) to be applied for the immediate packaging for all multilingual packs routinely, unless an additional safety warning as per Art 54 or key technical information is required. At present the minimum particulars are linked in some guidance to a particular volume of container, whereas the actual space available is less where a multilingual pack is proposed and is proportional to the number of languages on the pack, therefore this accommodation is reasonable to maintain availability of

medicines. For monolingual packs, a limit, e.g. 50 mL, could be proposed in guidance, whereas more flexibility is required to facilitate multilingual packs.

Overarching guidance, including the key principles and recommendations for centralised, MR, DC and national procedures for multilingual packaging is considered desirable, for example, to include direction on the size of MAH logos in mock-ups relative to other text, avoidance of a multiplicity of company logos due to the inclusion of MAH and local representative logos and co-promotion/co-marketing partners for MS sharing multilingual packs (whether in the blue box or not), similarly one overarching product information template for CAPs and MRPs/DCPs might be helpful.

### **1.2.2. Common approaches to reduce national requirements**

Where MSs have different national requirements, and different approaches to the blue box such as national warnings and pictograms, these can inhibit the development of multilingual packs due to the risk of confusion for patients of different MSs (for example in multinational packs sharing the same language), and where there are space constraints (applicable to CAPs and NAPs). Furthermore, multiple pictograms from different MSs for the same issue can cause confusion. While pictograms should never replace text, and the complexity of establishing such pictograms is acknowledged, a separate guidance could be prepared which outlines a common set of EU pictograms, in line with the approach for veterinary medicines. Similarly, separate national warnings should not be required if the product information has been prepared in accordance with the requirements of the Directive and associated guidance. In addition, it is noted that the provisions of Art 57 are not clearly defined ("certain forms of labelling") and are currently interpreted differently for CAPs and NAPs/MRPs/DCPs. While for CAPs the "blue box concept" is restricted to the outer packaging as clarified in the NtA "GL on the packaging information of medicinal products for human use authorised by the Union", no such restriction has been implemented for NAPs/MRPs/DCPs. Consequently, the blue box requirements for NAPs/MRPs/DCPs include additional national requirements even for the immediate label and the package leaflet. This approach has an advantage that national requirements can be accommodated for these national authorisations, but where these conflict between MSs, this can limit the possibility of multilingual packs. Therefore, MSs are requested to reduce such national requirements where possible.

It is also noted that some MSs require administrative information such as a second national identification number (e.g. Nordic number) on the outer packaging which would be included in the blue box. While this could be accommodated by an article similar to the veterinary regulation Article 11.2: "*A Member State may decide that, on the outer packaging of a veterinary medicinal product made available in its territory, an identification code shall be added to the information required under paragraph 1. [...]*", the need for such extra information or other national requirements (e.g. price) on the outer pack should be carefully reviewed by MSs, as it may inadvertently restrict the possibility of multilingual packs either through space restriction or commercial considerations.

A review of QRD stylistic matters and appendices to the QRD template periodically may be useful to align MSs non-consensus positions.

A more radical proposal is that for initial supplies and fast entry of new products to the market (e.g. in case of pandemics and health emergencies), and for a limited period of time (analogous to COVID-19 labelling flexibilities), a global label product could be permitted which could have a shortened name on the packaging, the provision of the package leaflet separately, and omission of EU number. In agreeing such an approach, safe use in MSs must be considered at all times due to the potential complexity of new innovative medicines.

Serialisation, where a common serialisation approach (e.g. GTIN) is not used, can restrict multilingual packs. Although this provision is covered separately under the Falsified Medicines legislation, MSs/EMVO/NMVOs should be encouraged to promote alignment.

## Proposed solutions – in legislation

Mandate that MSs avoid issuing national legislation which would have an impact on product information outlined in Title V, e.g. introduction of capacity restrictions for minimum particulars in national legislation, or in the case of a potential safety issue identified, promote appropriate consultation of CHMP/PRAC to harmonise implementation across EU rather than implement national warnings. It is considered that MSs should endeavour to review existing legislation to allow better alignment with EU positions and updated guidance, e.g. for capacity restrictions as above.

Add under Art 65 of the Directive a reference to guidance on the implementation of Art 62 regarding pictograms, in which the agreed pictograms could be included.

Require 'exp' and 'lot' to be used to denote expiry date and batch number in all MSs, in line with veterinary regulation.

Add an article similar to the new veterinary regulation Art 11.2 to allow for an identification code to be added to the outer pack (e.g. Nordic number), if necessary.

Define a situation where a global label product could be permitted, e.g. linked to conditional marketing authorisation, pandemic products or other, in guidance prepared under Art 65 on the implementation of Art 63.

## Proposed solutions – in guidance

Apply a stricter interpretation of blue box requirements on the outer pack to limit the requirements to those in the Directive, as safety issues should be addressed within the common text. Remaining national requirements, although undesirable, could be added in a 'blue box concept' in the package leaflet of NAPs/MRPs/DCPs.

Reference to some additional national information (e.g. price, reimbursement conditions as per Art 57 of Directive 2001/83EC) may hinder the use of multilingual packs; an effort to harmonise all information could be made in the short or medium term.

Allow exemptions to the inclusion of blue box information (only available in QR codes or other electronic formats).

MSs should be strongly encouraged to pursue further harmonisation of positions affecting multilingual packs, for example harmonising non-consensus positions in the QRD stylistic matters document. Further agreement of common terms, e.g. standard abbreviations, or patient friendly terms for pharmaceutical form, would be helpful, as the relevant information will be present on the packaging, and a further translation of the term could be added in the package leaflet for specific MSs.

A list of common pictograms could be agreed across the EU in order to limit the number of national pictograms, whilst retaining the text explanation. These would be outlined in guidance, according to Art 65 on the harmonised provisions for the implementation of Art 62. The pros and cons are presented in a list format below due to their extensive nature:

<b>Pros</b>	<b>Cons</b>
Common agreed pictograms may aid understanding where there is a language barrier.	Difficult to agree on particular pictograms across EU based on experience (e.g. different views regarding comprehensibility and acceptability of the "pregnancy pictogram" discussed for valproate, and DRUID program on driving and medicines).

Variations of slightly different pictograms would not be added by separate MSs, taking up space and potentially precluding common packs.	Still prone to misinterpretation , accompanying text will always be required and will have to be translated in all languages in case of MLPs.
Where a pictogram has been mandated by a Commission decision, the same pictogram could be applied across all generics and originators.	Difficult to agree on areas/topics for which pictograms should/should not be used across EU based on experience (e.g. "driving pictogram(s)" – common and mandatory in some MSs, generally rejected by others).
Common pictograms are not intended as a replacement for text and could be further explained in the PL.	Copyright issues will need to be taken into account unless mandatory pictograms are specifically created by EC/EMA/CHMP/PRAC/NCAs.
The mandated pictograms could be the subject of educational campaigns in EU as appropriate to aid understanding and acceptance (e.g. Internet Pharmacy label).	In case of "mandatory" pictograms, it will be necessary to clearly define for each pictogram in which cases the pictogram is actually mandatory (e.g. "pregnancy pictogram" - only in case of a contra-indication or already in case of one or more warning statements in the SmPC?).
A standardised statement or symbol relating to the scanning of QR code or use of URLs would be helpful in the context of electronic product information provision, to link from the printed information.	

Prepare guidance on global labelled products in response to the pandemic/health emergency situations defined, under Art 65 regarding harmonised provisions for the implementation of Art 63 exemptions.

MSs sharing multinational packs, where the same language is shared by two MSs, are strongly encouraged to continue bilateral discussions to align commonly used/legally defined terms (e.g. 'on medicinal prescription' in BE and NL).

MSs/EMVO/NMVO should be encouraged to standardise serialisation requirements, as where they differ this can impact on the preparation of multilingual packs.

### **1.2.3. Warning that the medicinal product must be stored 'out of the reach and sight of children'**

This requirement, although ideal, is not particularly relevant for products used predominantly in hospitals, e.g. parenteral products, and it occupies space that may be better used for critical information. Removal of this statement could be considered for CAPs and NAPs, including for monolingual packs.

#### **Proposed solutions – in legislation**

Include a definition of 'hospital only products' or 'healthcare professional administered products' in legislation and link an exemption to this designation, to permit that this statement is not required for products which will never be stored at home.

A concurrent update to Art 65 to refer to guidance on 'harmonised provisions for the implementation of Art 63' is also proposed.

## **Proposed solutions – in guidance**

The exemptions for 'hospital only products' or 'healthcare professional administered products' could be outlined in a Commission guidance in accordance with Art 65, regarding harmonised provisions for the implementation of Art 63. It is acknowledged that some regulatory issues could arise where a product range spans hospital and non-hospital situations, however a default option to include the statement in such cases could be outlined in guidance.

### ***1.3. Strengthen use of standards (e.g. ISO formats, e.g. for numbering)***

Differences in the format of the strength and numbering style in the name of the product due to national requirements may cause confusion for healthcare professionals and limit the possibilities for multilingual packaging, therefore further reference to standards may be appropriate. This is applicable to CAPs and NAPs.

The use of patient friendly terms for pharmaceutical forms is encouraged to reduce the length of the name of the medicine, in particular for products self-administered by patients.

Also, currently the Falsified Medicines Directive is limiting the opportunity for repackaging in smaller markets, where different unique identifiers persist across MSs.

When the ePI project is finalised, any specified technical requirements for the PI should be used (see separate section 2 on electronic product information).

## **Proposed solutions – in legislation**

MSs should be strongly recommended to use ISO guidance, e.g. for formatting numbers (i.e. long sequences of digits should be separated into groups of three digits by a space. For example, one thousand would be written as 1 000 and one million as 1 000 000. Such groups of digits should never be separated by a comma or a point, as these are reserved for use as the decimal sign). Text in the product information should use relevant ISO standards, in particular on labels of multilingual packs, which should facilitate marketing in multiple MSs.

Mandating the use of one system of unique identifier (e.g. Global Trade Item Number [GTIN]) under the Falsified Medicines Directive would avoid the impact of different approaches to serialisation precluding multilingual packs.

Mandating the use of patient friendly terms on labelling, as developed by EDQM, will shorten text and facilitate multilingual packaging.

## **Proposed solutions – in guidance**

EDQM should develop further patient friendly terms, e.g. for pharmaceutical forms, for use in the product name and they should be accepted for pharmaceutical forms and routes of administration, where appropriate, without the need to ask for case-by-case exemptions. Common abbreviations of these patient friendly terms may facilitate multilingual packaging if well understood, and such an approach could be further considered, e.g. by EDQM.

In the interest of consistency, guidance (for example under Art 65 relating to Art 63) should strongly recommend the use of standards, e.g. ISO, and agreed terms, and any standards conflicting with MedDRA should be realigned. It is noted that further consultation will be carried out shortly to establish MSs positions through QRD, which it is hoped will further clarify and harmonise MS positions.

## 1.4. Name issues

Several areas regarding the interpretation of the Directive requirements cause difficulties for the preparation of multilingual packaging, as they result in different names per MS and thereby preclude a pack common to several MSs. This arises for MRPs/DCPs. The pros and cons of proposed changes are outlined, where necessary, under the individual sections.

### 1.4.1. Omit need for MAH in name from legislation

Under Directive 2001/83EC Article 1.20 the name of the medicinal product is defined as: *The name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or the name of the marketing authorisation holder.* The requirement for the common or scientific name to be accompanied in the name by the trademark or name of MAH limits the possibility of multilingual packs, in particular for MRPs/DCPs, e.g. where different company styles would need to be applied for the MAH name in different MSs (e.g. B.V., D.A.C), or where the same product, e.g. as approved under MR/DC procedure, is marketed by different MAHs in different MSs. Different approaches to this issue are being currently taken by MS. It is noted that correct identification of the product in human readable form (by eye) is considered critical in case of product defects or medication errors, i.e. where name of product and batch number should be recorded for pharmacovigilance purposes, and patient safety should be maintained. Product distinction is generally achieved by using a unique invented name or a unique generic name. However other identifying factors would also be used, e.g. batch number in case of product recalls.

### Proposed solutions – in legislation

Several options are provided for consideration:

1. **Emphasise trademark option to MAH**, and encourage MAHs to cooperate or share the use of one trademark for the identical medicine for which a multilingual pack is required, which could, if necessary, be explained in the package leaflet linked to MAH. A wider use of trademark instead of MAH name in generic naming will facilitate preparation of multilingual packs, as the product name can be the same also if the product is marketed under different MAHs. Such a trademark should fulfil the need for a unique generic name and not be promotional or misleading.

**Example:** use *Losartan Brand* in two MSs instead of *Losartan Company and Losartan Company Nederland B.V.* respectively, for a product from the same procedure.

This use of a trademark is acceptable under current legislation.

2. Use of different company names in different MSs can be solved also by using the **core part of a MAH name** and exclude additions of company forms.

**Example:** use *Losartan Company* instead of *Losartan Company Nederland B.V.*

It is presumed this use of a core part of the name is acceptable under current legislation.

### Pros and cons for options 1 and 2

**Pros:** Higher level of availability through facilitated multilingual labelling. Keeping quick, simple and safe identification of a product by "name, strength and form". Inclusion of MAH details or neutral trademarks may improve transparency, safety follow-up. From the patient's perspective, the need to differentiate generics from one another, including throughout the supply chain, is met.



**Cons:** None known, yet.

### **3. Remove the requirement for the name to be accompanied by the name of the MAH.**

The name of the MAH will be present on the pack accompanied by the address, as per Title V of Directive 2001/83EC, and the marketing authorisation number and batch numbers are definitive. Excipients with action or effect are stated on the pack. Dispensing software usually lists the MAH for a particular product in the same field of vision. If there is a requirement for the product to be clearly distinguished for the patient, e.g. in the case of narrow therapeutic index drugs, anti-epileptics, then an invented name can always be applied.

**Example:** Losartan 50mg tablets .....MAH Company

### **4. Maintain the requirement of the name but allow that the outer and immediate package do not have to contain the full name, i.e. refer only to INN.**

This approach may facilitate certain databases which use the MAH in the name as a distinguishing factor rather than the MAH or authorisation number field, and also facilitate multilingual packaging. The approach to the name would need to be explained in the header of the package leaflet.

**Example:** *SmPC* Losartan Company  
*Label* Losartan

### **Pros and cons for options 3 and 4**

**Pros:** Higher level of availability through facilitating multilingual labelling. Limits discussions on long, promotional or misleading MAH names. Reduction in name change variations during MAH transfers (relevant to Option 3).

**Cons:** Loss of quick, simple and safe identification of a product by "name, strength and form". There is a need to differentiate generics from one another throughout the supply chain, for pharmacovigilance purposes and for communication between healthcare professionals and patients.

Removal of MAH details from name may affect transparency and safety follow up, and lead to issues at the levels of prescribing and dispensing. From the patient's perspective, generic bioequivalence criteria are based on population data, while differences between generics can be important for patients on the individual level as generics vary in composition and manufacturing. Similarly for drugs with a narrow therapeutic index or toxic molecules (e.g. anti-epileptic drug), switching from one generic to another should be avoided and a correct identification of the medicinal product is therefore essential if a generic-style name is used. It should be noted that the Name Review Group for centralised medicines strongly disagrees with Options 3 and 4 for the reasons mentioned above.

A concern has been raised that it should be warranted in the intellectual property legislation that the INN name cannot become proprietary even as name of the medicinal product. The Commission could review this point as part of this update, although it is noted that WHO are responsible for the selection/publication of the INNs.

### **Proposed solutions – in guidance**

It is considered that the necessary information on the MAH will be available on the pack, package leaflet and in databases linked to the authorisation number.

MAHs and MSs should be advised to consider the impact of their naming conventions on the potential for multilingual packs.

Emphasise the use of the trademark option to MAHs where multilingual packs are proposed, and reiterate that multiple MS's MAHs can still be retained on the pack (in the MAH section).

### **1.4.2. Use of INN of active moiety in name rather than INN + salt**

The benefit of adding salt to the name where it is not relevant (e.g. where not pharmacologically different) is questionable. It could jeopardise the use of multilingual packaging in case MSs follow the principle differently also for national procedures. Moreover, the name INN+salt is definitely longer than INN and would not fit in the limited labelling space. It should therefore be requested that new originator products are **formulated** with a strength corresponding to the active moiety and not the salt. If not, the INN underneath the name, strength, form on labelling should be that relevant to the strength in the name and it could be further omitted if the strength relates to the active moiety only. The use of an invented name (or reintroducing MAH trademark into name) could be recommended if a multilingual pack of a product containing strength expressed as a salt is proposed.

It should also be pointed out that (in some existing situations where the salt is not pharmacologically different) it is no longer requested that the name is reflecting the actual content of the active ingredient, e.g. *Losartan (MAH) 50 mg tablet contains 50 mg of losartan potassium*. This may be useful for multilingual packs.

### **Proposed solutions – in legislation**

The legislation does not mandate the inclusion of the salt form.

### **Proposed solutions – in guidance**

The CMDh BPG on multilingual packaging currently states: *It is expected that originator products are formulated having a strength in the name relating to quantity of active moiety and not the quantity of salt. This will avoid translation issues regarding the statement of the salt, and will simplify the agreement of multilingual packages. Further guidance on the expression of the INN within the name of the product and current MS agreements is available in the QRD stylistic matters. Such an approach could be further communicated to HCP and patients in the SmPC or package leaflet as necessary.* It is considered that this recommendation should be further communicated through scientific advice meetings and NRG guidance, and potentially reiterated in guidance for Art 63 regarding multilingual packs.

Recent NRG discussions, consequent to which the NRG guidance is under review, clarified that *only INN+salts/INN+esters with pharmacological activity should be reflected in product names* should also be helpful to limit this issue arising. It is stated by NRG that *if the salt or ester does not contribute to the pharmacological activity of the INN, the product name should be stated as INN. Likewise, the strength should reflect that of the pharmaceutically active component.* This will need to be further communicated.

### **1.4.3. Remove need to have the same name for all MSs for generics of CAPs**

Although not specifically linked to multilingual packaging, a further improvement relating to names is proposed in this section which will improve the handling of **MR/DC** procedures. This is therefore also relevant to Concept Paper 1 and will also be impacted by the outcome of discussions in Concept Paper 2. The current legislation states that generics of centrally authorised reference medicinal products should be authorised under the same name in all MSs concerned in MRPs/DCPs. This requirement, affecting MR/DC procedures, requires a significant amount of resources and

correspondence between MSs and the MAH during the timelines of the procedure in order to agree a common name. The advantage of this approach is not clear for invented names and the issue may be compounded if an INN name is proposed, where the use of a company style, e.g. B.V., D.A.C., and the spelling of the INN in different languages also needs to be accommodated.

If the purpose is for a patient to recognise a product when visiting another MS, for generics this is not considered relevant, as the active substance is normally sufficient. For MRPs/DCPs, the name of the product in each MS is currently mentioned in the package leaflet, although this requirement is proposed to be reviewed. Moreover, most generics are authorised nationally without having the same agreed name throughout the EU, so there is no need to single out generics of CAPs.

In MRPs/DCPs the product name is, and has to be, a national decision as it has to take into account national specificities like the local language, national naming policies, names of already authorised products, etc. It cannot always be solved by having an INN + MAH name, as there may be situations where one MS requires an invented name for a certain type of product, while another MS requires an INN + MAH name. Agreeing on the same name causes a lot of difficulties during procedures, so this obstacle should be removed.

## **Proposed solutions – in legislation**

Art 3.3(c) in Reg. 726/2004 is proposed to be removed:

*3. A generic medicinal product of a reference medicinal product authorised by the Union may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under the following conditions:*

*(a) the application for authorisation is submitted in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC;*

*(b) the summary of the product characteristics is in all relevant respects consistent with that of the medicinal product authorised by the Union except for those parts of the summary of product characteristics referring to indications or dosage forms which were still covered by patent law at the time when the generic medicine was marketed; ~~and~~*

*(c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made. For the purposes of this provision, all the linguistic versions of the INN (international non-proprietary name) shall be considered to be the same name.*

## **Proposed solutions – in guidance**

Remove the following requirement from NTA: “where a generic of a medicinal product through the centralised procedure is authorised by the competent authorities of the Member States in accordance with article 10(1) of the Directive 2001/83/EC, the generic medicinal product has to be authorised under the same name in all Member States where the application has been made”.

It is noted that national spelling of INN is already allowed.

## **2. Facilitating electronic product information**

The provision of authorised electronic product information for EU medicinal products has been identified as a critical requirement to facilitate dissemination of medicines information to patients and

healthcare professionals, enable easier access to data contained within the PI by regulators and stakeholders, and potentially increase efficiencies in the administration of PI.

The increasing digitalisation of the health landscape has led to a focus specifically on the role of the paper package leaflet for medicines. The package leaflet is one component of the authorised product information (in addition to the summary of product characteristics and labelling) and is generally included as a printed paper copy in the medicines package.

Developments in recent years have highlighted situations in which authorised electronic package leaflets can be used for rapid roll-out of up-to-date, multilingual information, instead of paper or as a complement to paper, these include:

- In health emergency situations such as the current pandemic;
- For medicines used in a hospital setting;
- For medicines administered by healthcare professionals;
- To support mitigation of shortages;
- To support supply of medicines for small markets;
- For orphan medicines and ATMPs;
- To provide the patient with up-to-date safety information on their medicines.

However, while such an approach facilitates dissemination of product information in certain situations, it is dependent on a level of electronic literacy and access which may vary between and within MSs. Therefore, before being implemented, a discussion on electronic instead of paper package leaflets should be held.

## ***2.1. Accessing electronic product information***

The use of electronic package leaflets raises the question of how this information can be accessed by the patient, consumer and healthcare professional. Several mobile scanning and other technologies are in use or may be introduced in the future, including:

- QR codes, data matrix codes, bar codes (e.g. linear bar codes, 2D bar codes);
- Apps;
- URLs;
- Websites;
- Other innovative technologies such as near-field technology, virtual assistants, etc.

Practical questions remain for the use of these methods, such as how to communicate and provide them to patients and consumers in cases where they do not handle any medicine packaging. The use of various types of codes are still paper-based concepts, i.e. they still need to be printed somewhere. The existence of an electronic package leaflet is not useful if patients do not know that it exists and how to access it.

It is essential that patients have full access to the package leaflet of their medicines without delays or interruption, and systems should be robust and validated and take into account that devices (e.g. smartphone) may not be available. In addition, it must be ensured that the correct version of the package leaflet is provided to the patient.

The source of electronic package leaflets could be company or regulator websites, and separate guidance is needed for both to ensure provision of up-to-date authorised information.

## **2.2. Format of electronic product information**

Today, product information in the EU is provided in PDF format or HTML format and/or printed paper. The electronic formats are not harmonised across the EU and do not enable free flow of product information between systems across the European medicines network.

An ongoing project has recently established an EU ePI Common Standard for electronic product information (ePI). ePI is defined as authorised, statutory product information for medicines in a semi-structured format created using the common EU electronic standard. ePI is adapted for electronic handling and allows dissemination via the world wide web, e-platforms and print. The EU ePI Common Standard is [published](#) and the standard includes a link to SPOR (master data systems for EU medicines). The ePI project will next enter a pilot phase, followed by implementation. Therefore, ePI will likely be implemented for some EU medicines at the timepoint when the revision of the pharmaceutical legislation comes into force. The legislation should therefore mandate the EU ePI Common Standard (including future versions of the standard following further development of the structured format), and thereby support harmonised ePI providing maximum benefits to EU citizens, healthcare systems and healthcare providers.

## **2.3. Proposals considered**

The following proposals have been put forward for consideration, and the aspects in favour or against these proposals are detailed below:

### **Implications of replacing paper with electronic package leaflets**

Electronic package leaflets could replace paper, in MSs that are technically more advanced implementing initially, and it should remain the MS competence to decide regarding provision on their market, including where a multilingual package leaflet is proposed. It would be the responsibility of the MAH to ensure that the product information is available to the patient and/or health care provider in an appropriate format agreed by the MS, e.g. facilitated by QR codes, open websites, or dedicated personal health accounts, and that the information provided is maintained aligned with agreed statutory information. It would also be the obligation of the MAH to provide a paper package leaflet to the patient on request. The use of electronic tools could be supported by educational campaigns. The introduction of the electronic package leaflet could be gradually performed in which the printed paper and the electronic leaflet coexist for a reasonable period of time, supported by educational campaigns. Electronic tools, such as QR code, data matrix (different to the data matrix used for serialisation), or barcodes could be included in the outer or inner packaging. It should be clear to users where a package leaflet has been intentionally omitted from a pack (e.g. on the package, within the pharmacists system or similar). It also should be considered that the appropriate package leaflet for a marketed box of a medicine may not be the same as the last updated one, with potential implications for administration of the medicine.

Legal measures could be considered to increase availability of and familiarity with electronic product information among the general public, with focus on patients (e.g. regular/mandatory inclusion of the URL to European or national platforms providing ePI where available).

Environmental concerns due to the paper used by having mandatory paper package leaflets would be an argument in favour of this proposal. However, we are not aware of an environmental impact analysis that directly compares the environmental impact of paper package leaflets with, for example,

the potential environmental impact of printing at pharmacies/elsewhere and server use for provision of electronic versions.

Measures should be considered to ensure that a paper version of the package leaflet is made available to those who need it. However, printing of package leaflets would be a huge burden on community pharmacists, could impact their regular services, and could be prone to errors (e.g. mixing up of package leaflets, especially in poly-medicated patients). Several MSs consider it is not acceptable to hand over the responsibility for printing package leaflets to pharmacists and/or health care staff in hospitals.

The concept of user testing would need to be adapted, as there will be a need for more options for layout testing. Layout testing, findability and understandability would still need to be tested for electronic versions. In addition, the implications on co-packaged products (in view of the medical device regulation) would need to be considered.

Pilot programs are ongoing in some MSs, e.g. BE-LU and ES, on the use of electronic package leaflets only in the hospital setting. It is also proposed to run a pilot for medicinal products used outside hospital setting from sharing experiences and best practices for an EU harmonised ePI or 'electronically displayed package leaflet only instead of paper package leaflets' strategy.

It is noted that a printed package leaflet is absolutely necessary for patients not familiar with the use of mobile scanning technologies, with low digital literacy, or low levels of internet access. The number of such patients that need to have paper package leaflets will vary between MSs. Availability of paper leaflets should be secured for those who need it, and it may not be the right time to abandon paper package leaflets if this puts patient groups that are not advanced in information technology at a disadvantage.

### **Implications of replacing paper with electronic package leaflets for specialised medicinal products**

Electronic package leaflets could be allowed for certain types of medicines such as ATMPs, 'hospital use products', 'healthcare professional administered products', or orphan medicines, and in case of health emergencies.

Electronically displayed package leaflet only instead of paper package leaflets should be facilitated by mobile scanning technology. Of note, the implementation of QR codes in the labelling, package leaflet and vaccination reminder cards of COVID-19 vaccines to access the product information has marked a milestone in the use of electronic tools for this purpose, having the most updated version of the package leaflet available and considering environmental aspects, in addition to the limited storage space in vaccination centres.

In 'hospital only products', the use of paper package leaflets is very limited. In many cases, these package leaflets are discarded together with the outer packaging, leaving only the medicinal product in its immediate packaging. In these cases, the information on the medicinal product is consulted online. Therefore, the suppression of printed copies in this situation should not entail problems with regard to the availability of the package leaflet.

For orphan medicines and ATMPs, it might be justified to allow electronic package leaflets only instead of paper package leaflets in order to facilitate supply to small markets. It might also be that the target patient group is well educated in their rare condition and are used to using electronic information, even in English only. However, the necessary analysis to support these assumptions may not be available, and inclusion of orphan medicines and ATMPs in this exemption might be premature. There is a significant risk that undue pressure would be placed on national competent authorities in MSs with

small markets to accept electronic package leaflets only. It should be considered how small markets can be protected from pressure to omit the paper leaflet.

For healthcare professional administered products, it is expected that the same issues as mentioned with printing of package leaflets by healthcare professionals could arise, as patients may request the package leaflet in paper from the healthcare professional.

Currently prescription requirements are also defined by each MS, so it is difficult to grant an exemption at EMA level based on prescription status. There would also be difficulties in connection with some national legislation which allows companies and individuals to choose how – in paper or electronic – to submit/receive documentation to/from national competent authorities.

### **Defining 'hospital only products' in legislation and linking exemptions allowing use of only electronic package leaflets to this definition**

Any definition of 'hospital only products' should be formulated in such a way that it could be used in data systems (marked-up in SPOR, etc). The definition could also include medicines not intended for self-administration i.e. 'healthcare professional administered products' (see also previous topic on multilingual packaging).

The use of mobile scanning or other technologies should be also gradually expanded in future for all medicinal products, not only for only 'hospital only products' or hospital packs.

### **Following the example of the veterinary regulation**

The veterinary regulation 2019/6, Article 14(3), allows MSs to decide whether the package leaflet shall be made available on paper or electronically, or both. This approach allows flexibility on a per product or a per MS basis, where there is a need to maintain accessibility to patients with diverse abilities. The regulation for human medicinal products could be amended to include an article analogous to the veterinary regulation, which could apply when the EU ePI Common Standard is operational. The considerations mentioned above regarding challenges of implementation and undue pressure on authorities apply to this option. In addition, it should be noted that use of veterinary medicines and use of human medicines are not directly comparable.

### **Legal basis for mobile scanning technologies**

The inclusion of QR codes on the packaging or package leaflet of human medicinal products is currently being supported by the Article 62 of Directive 2001/83/EC. However, a clear legal basis for QR codes, mobile scanning, or other technologies to be displayed on the packaging or package leaflet of medicines should be created.

It must be ensured that an electronic only package leaflet remains freely available and easily accessible for at least the great majority of the European population for the whole lifecycle of the medicine. While it is not possible for legislation to determine one or more particular type(s) of technology, it must be taken into consideration that technology only works in the way it is supposed to do, if the user (i.e. in this context the patient) knows how to correctly use the respective technology and is technically equipped to use it. Both conditions must be fulfilled to ensure that an electronic only package leaflet can fulfil its purpose, i.e. providing statutory information to the patients. Consequently, a suitable technology and a robust system must be chosen for providing an electronic only package leaflet.

## **2.4. Proposed solutions – in legislation**

Taking into account the above-mentioned considerations, it is proposed to amend Art 58 to allow provision of information through mobile scanning technologies in specific cases, e.g.:

1. The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is ~~directly~~ conveyed on the outer packaging or on the immediate packaging *or conveyed by other means as agreed by the Member State where the medicinal product is placed on the market.*
2. *Member States may decide that the package leaflet shall be made available on paper or **electronically**, or both.*
3. *Package leaflets made available electronically must comply with the EU ePI Common Standard once this standard is operational.*

However, should the proposals be pursued to enable electronic package leaflet only, with the decision at MS level, it should be noted that many authorities and stakeholders are not in agreement, readiness of authorities is not assured, undue influence may be given to pharmaceutical industry, undue pressure placed on authorities, and there is possibly introduction of a disadvantage to users who rely on paper package leaflets, depending on their MS. The burden of provision of a paper package leaflet where required should be borne by the MAH.

By deleting the term 'directly' from the phrase "**directly** conveyed on the outer packaging or on the immediate packaging", the provision could be interpreted as having the information conveyed via a QR code or other electronic means.

An unambiguous legal basis for QR codes, mobile scanning or other technologies to be displayed on the packaging or package leaflet of medicines should also be included in the legislation. This could be linked to the development of a pictogram under proposed update to Art 65 referencing Art 62.

A definition for 'hospital use products' and 'healthcare professional administered products' and for medicines used in a health emergency context should also be developed and included in the legislation, further to which relevant Commission guidance could be prepared under Art 65 referencing Art 63.

By referring to the EU ePI Common Standard in the proposal above, compliance to the standard, once operational, is supported. In addition, it is proposed to include text analogous to Art 57(2) of Regulation (EC) No. 726/2004 that would mandate applicants to submit ePI complying with the EU ePI Common Standard once this is operational and once it is required to be submitted to the EMA and national competent authorities.

The corresponding implications of changes to inclusion of paper package leaflet for Art 67 (radiopharmaceuticals) should be considered (separately) whether situations arise where the package leaflet details could be conveyed through a link to electronic product information.

## **2.5. Proposed solutions – in guidance**

The EMA/CMDh guidance on mobile scanning and other technologies should be revised in accordance with the changes made in the legislation. In addition, the guidance is proposed to be updated with further clarifications for assessors and this is under discussion.

There is currently no provision in the legislation about the format in which PI annexes are to be provided, however there is relevant EMA guidance on that aspect, i.e. PI annexes must be submitted in MS Word or PDF format. In order to encourage or mandate, as appropriate, the use of the EU ePI



Common Standard, the relevant EMA guidance documents should be revised accordingly once the standard is operational.

### **3. Language exemptions on printed materials (according to Art 63.3)**

The current legislation regulates the information contained in the labelling and package leaflet and the **languages** in which it must be written on the final materials that are to form part of the final medicinal product, being compulsory to be written in an official language of the MS where the medicinal product is placed on the market.

Article 63.3 permits applicants to request omission of certain particulars (labelling exemptions, which are dealt with in Section 1 above) and exemption from language requirements in line with Art 63.3, therefore not required to provide printed translated labelling components including package leaflet (i.e. **language exemptions**, as discussed below). This is separate to the linguistic review and translations issues outlined in Section 5 of this concept paper.

It is considered that the use of language exemptions should be exceptional, less preferable than the use of multilingual packs or labelling exemptions, and availability issues must always be weighed against the need for safe and correct use of medicines. Full language exemptions should not be used for commercial reasons only, i.e. justified only by cost reductions for industry. Notwithstanding language exemptions are currently used in practice as follows, however there is a scope for further refinement:

Language exemptions based on Art 63.1 are currently applicable to the outer labelling of orphan medicinal products and they are currently handled by the QRD Group (or are nationally addressed where no consensus is reached).

Language exemptions based on Art 63.3 are applicable to the printed labelling (outer and/or immediate) and package leaflet of medicinal products. Companies developing human medicines that are not delivered directly to patients or where there are availability issues may be exempt from some of the obligations for labelling or package leaflets. Such exemptions are currently handled by the QRD Group (CAPs) or at national level (some CAPs and nationally authorised products)

This separate consideration of orphan and non-orphan medicines in legislation (Art 63.1 v Art 63.2+3) has resulted in a quite complex process for handling language exemption requests for orphan products.

With the advent of the COVID-19 pandemic, flexibilities in relation to labelling and packaging requirements have been expanded to the authorised vaccines, as well as new therapies against COVID-19 in order to facilitate the rapid deployment at large scale during the pandemic, on a temporary basis. The execution of a quick and effective common approach has brought to light the need of having the appropriate tools to handle future similar situations, such as future pandemics, outbreaks or severe availability problems.

Considering all these aspects together, it is necessary to amend the scope of these **language exemptions** and to simplify the procedure of handling them as follows:

The scope of Art 63.1 for orphan medicinal products should be aligned with the scope of Art 63.3 for non-orphan medicines, i.e. expanded to all packaging components (i.e. outer and/or immediate label and/or package leaflet), therefore facilitating a common legal basis for language exemptions applicable to orphan and non-orphan products alike would be possible.

If considered further necessary and useful, legislation could provide particular considerations for “very specialised products”, e.g. orphan medicinal products as defined in Regulation (EC) No 141/2000, ATMPs as defined in Regulation (EC) No 1394/2007, and medicinal products intended to be used in the context of pandemic/threats/emergency situations, currently lacking a legal definition. However, particular considerations for these products could also be addressed in accompanying guidance only.

Language exemptions (relating to the printed labelling and package leaflet as per Art 63.3) could be expanded to be applicable to medicinal products used at hospital setting, for ‘healthcare professional administered products’, and in situations where severe availability problems are foreseen, or product for use in pandemics or health emergency situations where it is not possible to have the labelling printed in each official language. Other situations which would therefore become generally included under this exemption would be orphan medicinal products, ATMPs for autologous use or those medicinal products with a very short shelf life. No separate provision for orphan medicines in Art 63.1 would be required as outlined above. Full or partial EN only language exemptions could be permitted for the printed materials, where the safe and correct use of the product is not impacted, e.g. ‘healthcare professional administered products’, and could be supported by electronic available PI.

Furthermore, expanding the scope of **language exemptions** to ‘healthcare professionals administered products’ or ‘hospital use products’ will also be helpful to maintain availability. For example, this would allow partial exemptions, hence avoiding the need for translation of the INN in all languages (where confusion is unlikely), which could facilitate MLP or EN-only packs or situations where the package leaflet in the national language is not required in the pack (linked to provision of package leaflet electronically). It is acknowledged that these language exemptions and associated conditions and situations should be clearly and precisely defined for optimal use (e.g. considerations could include low number of patients expected to be treated, products with a very short shelf-life, specially trained patients, exemptions based on medical/technical or public health grounds, e.g. availability). Such language exemptions may be granted on a temporary basis by MSs and may be reviewed periodically. A review clause to allow an opportunity for re-evaluation of temporarily granted language exemptions should therefore be incorporated in legislation for use by authorities as necessary.

Regarding language exemptions (e.g. EN-only) for the package leaflet, one of the best approaches to resolve the language requirement exemptions requests is the inclusion of a QR code or other mobile scanning technologies, linked to a web which leads to the package leaflet in all the official EU languages. Another approach for the COVID-19 vaccines and therapeutics was the provision of the printed national package leaflet alongside with the packs (instead of included in the packs). Similar approaches could be applied to requests of exemptions in Art 63, since such tools should not be reserved only for the labelling flexibilities on COVID 19 vaccines, for which it has proven to be a success, but should be expanded for use in the critical situations mentioned above and outlined in guidance.

The approach to language exemptions could be applied for CAPs and NAPs. In the scope of MR/DC procedures, language exemptions (e.g. EN-only requests) are currently adequately handled nationally, however similar criteria could be considered. Further guidance could be developed regarding objective criteria and commonly agreed definitions in relation to language exemptions as necessary.

Considering the above mentioned reasons, the following modifications are proposed in legislation and in guidance. It is considered that these solutions are applicable to CAPs and MRPs/DCPs, however any particularities are outlined below as necessary.

### ***Proposed solutions – in legislation***

Amendments to **Article 63:**

Current legislation reads:

Article 63:

1. *The particulars for labelling listed in Articles 54, 59 and 62 shall appear in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

*The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.*

*In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community.*

2. *The package leaflet must be written and designed in such a way as to be clear and understandable, enabling users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

*The first subparagraph shall not prevent the package leaflet from being printed in several languages, provided that the same information is given in all the languages used.*

3. *Where the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

For the reasons previously outlined, it is proposed to modify Art 63.1 and Art 63.3 in order to **extend the scope of labelling and language exemptions** for the outer, immediate and/or package leaflet, as follows. It is considered that no separate accommodation would then be required for orphan products.

Proposed modification:

Article 63:

1. *The particulars for labelling listed in Articles 54, 55, 59 and 62 shall appear in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

*The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.*

~~*In the case of certain orphan medicinal products, the particulars listed in Articles 54, 55, 59 and 62 may, on reasoned request, appear in only one of the official languages of the Community.*~~

2. *The package leaflet must be written and designed in such a way as to be readable, clear and understandable, in terms that are comprehensible to the general public enabling users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.*

*The first subparagraph shall not prevent the package leaflet from being printed in several languages, provided that the same information is given in all the languages used.*

3. Where the medicinal product is not intended to be delivered directly to the patient i.e. hospital only products, healthcare professional administered products, medicinal products intended to be used in the context of pandemics/health emergency situations, or severe problems foreseen in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.

4. Where space constraints are foreseen on the printed materials of the medicinal product due to the small size of the pack/container/label dimensions or due to the necessity for displaying the same information several times in different languages to facilitate multilingual packaging the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.

5. Where the medicinal product is not intended to be delivered directly to the patient i.e. hospital only products, healthcare professional administered products, or medicinal products intended to be used/needed in the context of pandemics/ health emergency situations, or severe problems foreseen in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant a full or partial exemption to the obligation that the printed outer and/or immediate labelling and the printed package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive.

6. Such exemptions (as outlined in paragraphs x/63.3 and y/63.4 z/63.5 above) may be granted on a temporary basis by the Member States and may be reviewed periodically.

Amend **Art 58** to allow provision of information through mobile scanning technologies (linked to topic 2 in this concept paper), which would support language exemptions:

1. The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is ~~directly~~ conveyed on the outer packaging or on the immediate packaging, or conveyed by other means as agreed by the Member State where the medicinal product is placed on the market.
2. Member States may decide that the package leaflet shall be made available on paper or electronically, or both. Package leaflets made available electronically must comply with the EU ePI Common Standard once this standard is operational.

A similar change analogous to the veterinary regulation 2019/6 Article 14(3) could also be made: *The package leaflet shall be written and designed to be readable, clear and understandable, in terms that are comprehensible to the general public. Member States may decide that it shall be made available on paper or electronically or both.*

### **Proposed solutions – in guidance**

The scope of the labelling exemptions currently in Art 63.3 should be extended as outlined in the legislation proposal (Section 1) for CAPs and NAPs. Similarly, it is proposed to extend the scope of the **language exemptions** in Article 63. Therefore guidance according to Art 65 in relation to the implementation of Art 63 could be prepared. This could cover what types of products exemptions could be generally accepted, e.g. orphan medicines, ATMPs for autologous use, products with a short shelf life, 'hospital only products' and 'healthcare professional administered products' (the definition of which could include products for self administration by specially trained patients/ambulatory use) without impairing the safe and correct use of the product, thus providing some harmonisation (see also Section 1). The impact of language exemptions and pharmacovigilance requirements, e.g. educational

materials, should be carefully considered, and it is noted that widespread use of language exemptions is considered undesirable by MSs.

Such guidance could also link to other aspects such as cross-referencing to electronic product information (based on a fully functioning system), definitions, specific labelling exemptions, justifications, expectations, etc. Some examples of such guidance are outlined as follows: In case of language exemption of package leaflet request, the possibility of the inclusion of a QR code (or similar electronic tool) linked to a web which leads to the package leaflet in all the official languages and MS blue box information should be added in this section of the document of recommendations. It could be considered to routinely allow using the EN translation for some excipients, on multilingual packaging, so that they only have to be mentioned once, as full information will be in the package leaflet. However, this approach would need to be based on a careful review of the patient safety in order to avoid potential hypersensitivity reactions.

Additional practical guidance could further clarify the submission and contact points for these requests for language exemptions in light of the revision of the legislation proposed, for example, in the scope of the centralised procedure it will be necessary to introduce some modifications in the document "Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure" (EMA/135540/2019 rev.4\*)

## **4. User testing of generic medicines Package Leaflet**

Art 59.3 provides that "*The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use*".

Notwithstanding how important this issue is, and that user testing has been in place for many years assuring that all authorised medicinal products have complied with this requirement, it seems appropriate at this moment to eliminate or substantially reduce this requirement for generic medicinal products, maintaining it only for new non-generic medicinal products. This could allow a simplification of procedures and reduce burden for authorisation of these kind of medicinal products, which are becoming more and more common. Based on MSs experience, the user tests submitted with DCP applications very rarely lead to any changes in the package leaflets, thus limiting the review is possible.

### ***Proposed solutions – in legislation***

The appropriate requirements in legislation should be updated in line with this proposal, however it is considered that the wording of Art 59.3 is sufficiently broad to allow the proposal for limited user testing for generics to be expressed in guidance.

### ***Proposed solutions – in guidance***

The use of bridging for generics should be promoted. The appropriate guidance documents (e.g. QRD Guidance and Checklist for the Review of User Testing Results, QRD form for submission and assessment of user testing bridging proposals) should be updated in line with this proposal. For example, a bridging report regarding the company house style that has been user tested could be provided, along with confirmation that the text of the package leaflet is a copy of the originator package leaflet, and thus the key messages will already be present. Furthermore, the expectations for the printed package leaflet (e.g. type size and font, design and layout of the information, headings, print colour, syntax, style, paper thickness, and use of symbols and pictograms) are very well described in the Guideline on Readability. Thus, the user testing form/AR could be reviewed and significantly shortened for generics or alternatively it could be considered to replace it completely with

a declaration from the MAH that the package leaflet complies with all the requirements of the Guideline on Readability (for example including tick boxes confirming similarity of design and layout).

## **5 Linguistic review**

### ***5.1 Linguistic review for CAPs***

There is a request that the linguistic review for CAPs should be added to the legislation with a coordinating role for EMA to improve the quality and checking of translations. A comparable review may be undertaken for NAPs in the MR/DC procedure to determine whether these should also be covered.

#### ***Proposed solutions – in legislation***

A requirement should be added to the legislation that the applicant/MAH has to submit good quality translations of the product information. The linguistic review for CAPs should be added in the legislation, stating that it is the task of the EMA to coordinate the linguistic review and, in dialogue with industry and NCAs, to provide suitable timetables that promote translations of good quality.

#### ***Proposed solutions – in guidance***

Further update of guidance is required to diversify the timetable for linguistic review. The following issues need to be addressed:

The time given for MAHs to perform the translation is today extremely short, which has negative impact on the quality of translations.

As the number of CAPs increases year by year, the NCAs workload for linguistic review is also increasing. The time given for NCAs to review all CAPs translations is already too short. It puts a lot of strain on NCAs two weeks per month; it is difficult to allocate staff for two weeks per month. A more even workload would improve both working conditions and save resources.

The timetable running during summer season and winter holidays is not sustainable; it puts a lot of strain on all stakeholders.

It is acknowledged that extending the timetable for linguistic review (from 14 days) will affect other parts of the chain, e.g. Commission decision timetable, as the total duration cannot be exceeded, however such a revision and accommodation is indeed needed.

### ***5.2 Marketing authorisations without national translations***

It may be possible to separate the compliance check of the translation from the step of issuing a product authorisation, e.g. for MRPs/DCPs where the product is not going to be marketed or a particular language translation will not be marketed. This discussion concerning the translation of the Annexes at the end of procedures is separate from the discussion in Section 3 of this paper regarding Art 63.3 language exemptions. The translation of Product Information is mandatory for all marketed products, however it is currently a practice in some MSs (e.g. IS, NO, PT, DK) not to require translations for NAPs that are not going to be placed on the market, e.g. duplicates. In the case of MR/DC procedures, a legal basis for not requiring submission of translations for non-marketed products (e.g. duplicates) or non-marketed translations would be welcome.

Where unnecessary translations are avoided, extra network capacity remains available to deal with required translations and other workload. However, there should be an obligation to submit high-quality translations within a given timeframe to ensure the appropriate translated PI in due time before the medicinal product will be placed on the market. It is noted that this issue is also considered in Concept Paper 1.

## **Proposed solutions – in legislation**

The options to improve the legal basis for this action are as follows:

### **Option 1**

Add the following only to legislation:

*A MS may require a translation in one of their official languages only.*

### **Option 2:**

Add the following to legislation:

*Provision of the translation(s) of the Product Information is mandatory for all marketed products. A MS may require a translation in one of their official languages only. For non-marketed products, the applicant must provide a complete high quality translation for review prior to marketing.*

### **Option 3:**

Include in legislation in analogy to the veterinary regulation, e.g.:

*If the applicant fails to provide a complete high quality translation of the required documentation within an agreed period after having received the information referred to in Articles XXXX (dealing with end of procedures), the application shall be considered to have been withdrawn (unless the product is not marketed).*

*A MS may require a translation in one of their official languages only.*

Three options are proposed varying in complexity and need for MSs follow-up. While the request here is to avoid submission of unnecessary translations to better use network capacity, MSs would like to emphasise (potentially in legislation) that where translations are submitted, MAHs should be encouraged to provide high quality translations.

## **Proposed solutions – in guidance**

If the approach is agreed, the applicant should be advised to indicate in the cover letter if the product will not be marketed in a particular MS. Provision of high-quality translations should be re-emphasised. Advice on how to submit translations if the product is due to be marketed later on may also be required.

## **Annex 1**

### **Compilation of proposed legislative changes to Directive 2001/83/EC**

#### TITLE I

#### **DEFINITIONS**

##### Article 1

20. Name of the medicinal product: The name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or the name of the marketing authorisation holder.

#### TITLE V

#### **LABELLING AND PACKAGE LEAFLET**

Article 54 (d) *{after a review as proposed in Section 1.1 above}*

a list of those excipients known to have a recognized action or effect and included in the detailed guidance published pursuant to Article 65. ~~However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;~~

##### *Article 55*

1.

~~The particulars laid down in Article 54 shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.~~

2.

The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62.

- the name of the medicinal product as laid down in point (a) of Article 54,
- the name of the holder of the authorization for placing the product on the market,
- the expiry date,
- the batch number.

3.

The following particulars at least shall appear on ~~small~~ immediate packaging units *other than those referred to in paragraph 2*, on which the particulars laid down in Articles 54 and 62 cannot be displayed:

- the name of the medicinal product as laid down in point (a) of Article 54 and, if necessary, the route of administration,
- the method of administration,
- the expiry date,
- the batch number,
- the contents by weight, by volume or by unit.



#### Article 58

1. The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is ~~directly~~ conveyed on the outer packaging or on the immediate packaging *or conveyed by other means as agreed by the Member State where the medicinal product is placed on the market.*

2. Member States may decide that the package leaflet shall be made available on paper or **electronically**, or both.

3. Package leaflets made available electronically must comply with the EU ePI Common Standard once this standard is operational.

#### Article 59 (g) {after a review as proposed in Section 1.1 above}

1.

The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order: [...]

(g)

~~where the medicinal product is authorised in accordance with Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State;~~

#### Article 63

1. The particulars for labelling listed in Articles 54, 55, 59 and 62 shall appear in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

~~In the case of certain orphan medicinal products, the particulars listed in Articles 54, 55, 59 and 62 may, on reasoned request, appear in only one of the official languages of the Community.~~

2. The package leaflet must be written and designed in such a way as to be *readable*, clear and understandable, *in terms that are comprehensible to the general public*, enabling users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

The first subparagraph shall not prevent the package leaflet from being printed in several languages, provided that the same information is given in all the languages used.

3. Where the medicinal product is not intended to be delivered directly to the patient *i.e. hospital only products, healthcare professional administered products, medicinal products intended to be used in the context of pandemics/health emergency situations*, or where there are severe problems *foreseen* in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.

4. *Where space constraints are foreseen on the printed labelling and package leaflet materials of the medicinal product due to the small size of the pack/container/label dimensions or due to the necessity for displaying the same information several times in different languages to facilitate multilingual*

*packaging the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.*

5. Where the medicinal product is not intended to be delivered directly to the patient *i.e. hospital only products, healthcare professional administered products, medicinal products intended to be used in the context of pandemics, health emergency situations*, or where there are severe problems foreseen in respect of the availability of the medicinal product, the competent authorities may, *subject to measures they consider necessary to safeguard human health*, grant a full or partial exemption to the obligation that the printed outer and/or immediate labelling and the printed package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive.

6. *Such exemptions (as outlined in paragraphs x/63.3 and y/63.4 z/63.5 above) may be granted on a temporary basis by the Member states and may be reviewed periodically.*

#### Article 65

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

(a)

the wording of certain special warnings for certain categories of medicinal products;

(b)

the particular information needs relating to non-prescription medicinal products;

(c)

the legibility of particulars on the labelling and package leaflet;

(d)

the methods for the identification and authentication of medicinal products;

(e)

the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated;

(f)

harmonised provisions for the implementation of Article 57;

(g)

harmonised provisions for the implementation of Article 62;

(h)

harmonised provisions for the implementation of Article 63.

#### Article 67

The competent authority shall ensure that a detailed instruction leaflet is enclosed with, *or conveyed on* the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with the provisions of Article 59. In

addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

→ An article will be needed related to handling of translations as outlined in Section 5 of the concept paper.

### **Proposed change in Regulation 726/2004**

Art 3.3(c) is proposed to be removed.

*3. A generic medicinal product of a reference medicinal product authorised by the Union may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under the following conditions:*

*(a) the application for authorisation is submitted in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC;*

*(b) the summary of the product characteristics is in all relevant respects consistent with that of the medicinal product authorised by the Union except for those parts of the summary of product characteristics referring to indications or dosage forms which were still covered by patent law at the time when the generic medicine was marketed; ~~and~~*

*~~(c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made. For the purposes of this provision, all the linguistic versions of the INN (international non-proprietary name) shall be considered to be the same name.~~*

## 13. Concept Paper for the EC on **Safety and Pharmacovigilance**

### DISCLAIMER

As part of the consultation process leading to the pharmaceutical reform, experts from the European Medicines Agency and from national competent authorities (under the umbrella of the Heads of Medicines Network) drafted at the request of the Commission a series of ‘concept papers’ on technical aspects, based on their experience with operating under the current pharmaceutical legislation to inform the Commission services during the preparation of the legal proposals.

The views expressed in these concept papers are the product of experts’ reflection process on different possibilities, they do not necessarily represent positions of the organisations to which these experts are affiliated and may not be quoted as such. For the preparation of its legal proposals, the Commission took into account the options presented in the concept papers as part of the total available evidence.

Topic leads	<i>Experts from EMA</i>
Drafting group	Experts from CHMP, PRAC and EMA

### Summary

Based on almost ten years’ experience with the 2010 pharmacovigilance legislation in force since July 2012, assessments of risks and risk minimisation measures conducted within this legal framework as well as recent and expected developments in pharmaceutical industry and healthcare, this Concept Paper suggests simplifying and strengthening some of the pharmacovigilance-related aspects of the legislation, in particular with a view to:

- Action Area A: Improving pharmacovigilance systems of marketing authorisation holders, taking into account their global environments and needs for business continuity
- Action Area B: Streamlining regulatory procedures for focus and efficiency of pharmacovigilance, taking into account risk-proportionality
- Action Area C: Enhancing effectiveness of safety-related actions for patient and public health, taking into account changes in healthcare and opportunities for engagement with stakeholders.

This Concept Paper was drawn up with input from PRAC, CMD(h), PhVIWG and EMA, and took into account the EMA-PRAC Scoping Paper of 5 March 2021 for revising the Implementing Regulation.

#### Additional valproate-specific summary:

Among the assessment experiences informing this Concept Paper are the referral procedure for the teratogenic and adverse development risks of valproate in 2017/8, during which the first-ever EU public hearing was held<sup>1</sup>. This stakeholder interaction and risk assessment revealed delays in the dissemination of the previously required additional risk minimisation measures (aRMM) by the

<sup>1</sup> European Medicines Agency (EMA). Public hearing on valproate: first experience and lessons learnt. London: EMA; 2017. [https://www.ema.europa.eu/en/documents/report/public-hearing-valproate-first-experience-lessons-learnt\\_en.pdf](https://www.ema.europa.eu/en/documents/report/public-hearing-valproate-first-experience-lessons-learnt_en.pdf).

marketing authorisation holders (MAHs) as well as delays in the adoption of the measures in healthcare. A detailed analysis of the stakeholder input, underpinned by theories on implementation of innovation in healthcare, was conducted and provided suggestions to PRAC<sup>2</sup>. Considering this assessment experience, the Concept Paper calls for requiring MAHs to:

- Test aRMM with patients and healthcare professionals (see Action 27), to ensure that aRMM are legible, clear and easy to use;
- Notify competent authorities/PRAC systematically and regularly about the launch and dissemination status of aRMM (see Action 25), to enable competent authorities/PRAC to monitor this fundamental step for aRMM effectiveness; and
- Provide data on the population exposed to medicinal products in the EU (see Action 24), to support competent authorities/PRAC also in aRMM effectiveness monitoring.

Further, this Concept Papers asks the European Commission to investigate if a stronger legal basis for elements constituting pregnancy prevention programmes (PPP) of teratogenic medicines is possibly needed, in particular for the outer packaging labelling strongly called for by patient representatives (see Action 26).

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<sup>2</sup> Bahri P, Morales DR, A Inoubli, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel Analysing Stakeholder Safety Engagement Tool (ASSET). *Drug Saf.* 2021; 44: 193–209 (epub 30 Oct 2020). doi: 10.1007/s40264-020-01005-3.

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# Recommendations for change

## ACTION AREA A: Improving pharmacovigilance systems of marketing authorisation holders

### 1. Action 'Requiring corrective actions from the applicant after pre-authorisation pharmacovigilance inspections'

#### ***Problem statement***

- The current legislation attributes the responsibility for pharmacovigilance to MAHs (with one exception, i.e. the requirement to have in place a qualified person for pharmacovigilance (QPPV), which applies not only to the MAH but also already to the applicant<sup>3</sup>).
- However, pre-authorisation inspections frequently result in findings for corrective action where an applicant is not yet a MAH.
- It is considered a gap in the legislation that the applicant is not required to take corrective action, jeopardising that a fully functional pharmacovigilance system is in place at the time of granting a marketing authorisation for the medicinal product.

#### ***Problem solution – Proposed legal intent***

- It is proposed to extend legal pharmacovigilance responsibilities to the applicant with regard to putting in place core elements of the pharmacovigilance system prior to the submission of an application for marketing authorisation and taking corrective action as needed following pre-authorisation inspections (proposed to amend Article 8(3)(ia) of Directive 2001/83/EC).
- The core elements should be drawn from Article 2 of the Commission Implementing Regulation (EU) No 520/2012 and in particular include:
  - Outline of the organisational structure of the pharmacovigilance system with plans for resources and recruitment (i.e. for having in place a sufficient number of sufficiently trained persons);
  - Quality management system elements (i.e. training plans, a quality manual for key pharmacovigilance processes regarding risk management plans, individual case safety reports, periodic safety update reports, signal management, emerging safety issues, post-authorisation safety studies and risk minimisation measures).
- Corrective actions, when they are not essential to the pharmacovigilance activities and/or when they are not taken before the granting of the marketing authorisation, should become post-authorisation measures (PAMs) in the marketing authorisation.

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<sup>3</sup> Article 8(3)(ia) of Directive 2001/83/EC: "A summary of the applicant's pharmacovigilance system which shall include the following elements:  
- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,  
- the Member States in which the qualified person resides and carries out his/her tasks,  
- the contact details of the qualified person,  
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,  
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept."



## **Problem solution – Proposed guidance**

The new legal provisions would be further detailed in GVP Modules I and III.

## **2. Action ‘Strengthening the MAH’s contractual arrangements with pharmacovigilance subcontractors for quality management’**

### **Problem statement**

- Current legal provisions require MAHs which subcontract certain activities of the pharmacovigilance system to third parties to draw up contracts describing the arrangements for delegation and the responsibilities of each party.<sup>4</sup>
- MAHs very often subcontract pharmacovigilance activities in whole or in part. During pharmacovigilance inspections an increasing amount of deviations have been identified in contractual arrangements, e.g. unclear descriptions of roles and responsibilities or lack of adequate text to allow management and oversight of the outsourced activities.
- It is considered that these shortcomings increase the risk of serious failures of MAH pharmacovigilance systems.

### **Proposed solutions – in legislation**

- It is proposed to complement current legislation on MAH pharmacovigilance quality management<sup>5</sup> with stronger requirements on compliance management of third parties by the MAH as well as ensuring that third parties can be audited (see Action 3) and be inspected for the pharmacovigilance activities that have been delegated (proposed to amend Article 104(3) of Directive 2001/83/EC<sup>6</sup>).

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<sup>4</sup> Article 6 of Commission Implementing Regulation (EU) No 520/2012:

*“1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.*

*2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned.” and*

Article 2(6) of Commission Implementing Regulation (EU) No 520/2012: [*“The pharmacovigilance system master file shall contain at least all of the following elements:”*] *“where applicable, a description of the activities and/or services subcontracted by the marketing authorisation holder in accordance with Article 6(1).”*

<sup>5</sup> Article 11 of Commission Implementing Regulation (EU) No 520/2012:

*“1. Specific quality system procedures and processes shall be in place in order to ensure the following:*

*(a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and appropriate measures are taken by the marketing authorisation holder;*

*(b) the scientific evaluation by the marketing authorisation holder of all information on the risks of medicinal products, as referred to in the second subparagraph of Article 101(1) of Directive 2001/83/EC;*

*(c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database within the time limits provided for in the first and second subparagraphs respectively of Article 107(3) of Directive 2001/83/EC;*

*(d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals in accordance with Article 21(2);*

*(e) effective communication by the marketing authorisation holder with the national competent authorities and the Agency, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;*

*(f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;*

*(g) appropriate communication by the marketing authorisation holder of relevant safety information to healthcare professionals and patients.*

*2. Where a marketing authorisation holder has subcontracted some of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.”*

<sup>6</sup> Article 104(3) of Directive 2001/83/EC: *“As part of the pharmacovigilance system, the marketing authorisation holder shall:*

- In line with the Commission Implementing Regulation (EU) 2021/1281 for veterinary medicinal products, the legislation could include the following:

The marketing authorisation holder, when delegating pharmacovigilance tasks, shall include in the subcontracts a clear description of the roles and responsibilities and the process in place to ensure third party(-ies) are in compliance with Title IX. The third party may not subcontract any task assigned to it by the marketing authorisation holder without the marketing authorisation holder's written consent. Any third party contracted to carry out activities in whole or in part on behalf of or in conjunction with a marketing authorisation holder, shall accept to be audited by or on behalf of the marketing authorisation holder and to be inspected by the Competent Authorities.

### ***Proposed solutions – in guidance***

The new legal provisions would be further detailed in GVP Modules II, III and IV.

## **3. Action 'Clarifying requirements for the MAH's pharmacovigilance audits'**

### ***Problem statement***

- Current legal provisions require the MAH to audit its pharmacovigilance system in a risk-proportionate manner.<sup>7</sup> It is, hence, expected that audits of high-risk processes are performed more often, while low-risk processes will be audited less frequently.
- However, inspection experiences show that many MAHs interpret the legislation to mean that third parties to whom pharmacovigilance activities have been subcontracted have only to be audited when the risk assessment indicates a high risk.
- This unclarity in the legislation results in large parts of MAHs' pharmacovigilance systems remaining completely unaudited, jeopardising effective quality management.

### ***Problem solution – Proposed legal intent***

- It is proposed to clarify the legislation, to ensure that the whole MAH pharmacovigilance system, including all its subcontracted activities, will be audited at regular intervals (proposed to amend Article 104(2) of Directive 2001/83/EC).

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(a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;

(b) maintain and make available on request a pharmacovigilance system master file;

(c) operate a risk management system for each medicinal product;

(d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;

(e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority and the Agency."

<sup>7</sup> Article 104(2), 2<sup>nd</sup> sent. of Directive 2001/83/EC: "The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed." and

Article 12 of Commission Implementing Regulation (EU) No 520/2012: "Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. Those audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited."

- New legal provisions may consider the wording in Article 8(1) of the Veterinary Implementing Regulation (EU) 2021/1281:

*"Marketing authorisation holders shall perform audits of the pharmacovigilance system at regular risk-based intervals to ensure that it complies with the requirements set out in this Regulation and to determine its effectiveness. The audits shall be planned to cover all pharmacovigilance activities for a defined period and verify their conformity with the policies, processes and procedures of the quality management system." and "Any third party contracted to carry out activities in whole or in part on behalf of or in conjunction with marketing authorisation holders, shall accept to be audited by or on behalf of marketing authorisation holders and inspected by the Competent Authorities."*

### ***Proposed solutions in guidance***

The new legal requirement would be further detailed in GVP Module IV, with regard to e.g. criteria for determining, in a risk-based manner, the length of time which may be acceptable to elapse between audits.

## **4. Action 'Requiring safety data exchange agreements as part of the MAH's contractual arrangements'**

### ***Problem statement***

- Current legal provisions require MAHs who subcontract certain activities of the pharmacovigilance system to third parties to draw up contracts describing the arrangements for delegation and the responsibilities of each party.<sup>8</sup>
- However, data transfer arrangements are not specifically mentioned in the legislation as part of these contracts, and inspection experience has shown that safety data collected by third parties may not be transmitted within appropriate timelines, not fully, or not at all.
- This might jeopardise the complete and timely management and monitoring of suspected adverse reactions occurring within and outside the EU by the MAH and result in delayed or incomplete submissions of data to EudraVigilance.

### ***Problem solution – Proposed legal intent***

- It is proposed to legally require, as part of the MAH's contractual arrangements, a safety data exchange agreement (SDEA), covering the contents which will be explained in GVP and specifically including the arrangements for exchange of ICSRs and reporting to EudraVigilance (proposed to amend Article 104(3) of Directive 2001/83/EC).

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Module II, including the following: When preparing a SDEA, all aspects of proper and reliable cooperation in the view of pharmacovigilance

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<sup>8</sup> Article 6 of Commission Implementing Regulation (EU) No 520/2012:

*"1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.  
2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned."*

obligations between the responsible parties should be considered and documented (e.g. extent of data, format, timelines, frequency, format, responsibilities, reconciliation method).

## **5. Action 'Requiring the MAH to draw contractual arrangements for pharmacovigilance with marketing partners'**

### ***Problem statement***

- MAHs frequently engage in partnerships with other companies for the marketing of their medicinal products, e.g. in a country outside the EU (also referred to as 'licensing partners'). The partnerships can be of diverse nature, e.g. a joint product development resulting in Partner A applying for a marketing authorisation outside the EU and Partner B applying for a marketing authorisation in the EU for the same product. Inspection findings show that pharmacovigilance information from these marketing partners may not be transmitted to the MAH in the EU and also no collaboration for other pharmacovigilance obligations may happen. The current legislation makes clear that the MAH in the EU shall have authority over and reporting responsibility to EudraVigilance for data from outside the EU if it is also the MAH outside the EU<sup>9</sup>. However, if the EU MAH is not the MAH outside EU, legislation is not clear whether exchange of safety information (e.g. individual case safety reports (ICSRs)) is required between the EU MAH and partners outside the EU.
- Differences in MAHs' interpretation of the legal requirements above occur despite the guidance in GVP Module IV<sup>10</sup>, which makes reference to the Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products (Ref.: [98/C 229/03](#)) (a similar definition of what is to be understood under same applicant/MAH can also be read in the Notice to Applicants).
- It is considered that the current legislation is unclear about whether the MAH in the EU (itself or its mother company) has to have MAH status outside the EU in order for the legislation to apply to non-EU data. The term "commercial agreement" in the Commission Communication may be too vague to allow for an unambiguous interpretation. It is hence considered that these unclarities jeopardise the conduct of pharmacovigilance by the EU MAH based on all worldwide evidence available for the product and jeopardise complete submissions of data to the EU regulatory network for assessment and decision-making.

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<sup>9</sup> Article 107(3) par. 1 of Directive 2001/83/EC: "Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event".

<sup>10</sup> GVP Module VI: "The marketing authorisation holder shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products authorised in the EU, is brought to its attention by any company outside the EU belonging to the same mother company (or group of companies) [Footnote: As outlined in the Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products (Ref.: 98/C 229/03)]. The same applies to the marketing authorisation holder when having concluded a commercial agreement with a company outside the EU for one of its medicinal products authorised in the EU. Pursuant to Article 107(1) of Directive 2001/83/EC, the marketing authorisation holder shall record those reports of suspected adverse reactions and shall ensure that they are accessible at a single point within the EU. The source data or an image should be easily accessible in order to be made available to competent authorities in Member States upon request (see VI.B.5. for guidance on quality management). The clock for the submission (see VI.B.7. for day zero definition) starts when a valid ICSR is first received by one of these companies outside the EU."

## ***Problem solution – Proposed legal intent***

- It is proposed that the revised legislation requires the MAH in the EU to have contractual pharmacovigilance arrangements in place, including a SDEA (see Action 4), with other MAHs - within and outside EU - with whom the MAH has entered into commercial contracts for the active substance concerned (irrespective of the strengths, pharmaceutical forms, routes of administration, presentations, authorised indications, manufacturing process, or names of the concerned medicinal product), in order to allow the MAH to fulfill their pharmacovigilance obligations defined in Title IX of Directive 2001/83/EC (proposed to amend Article 104(3) of Directive 2001/83/EC).
- In addition, with regard to Commission Communication 98/C 229/03, diversity in interpretation of applicability of the legal provisions at least to centrally authorised products and products authorised through mutual or decentralised procedures is proposed to be avoided in future legislation by explicitly covering purely nationally authorised products too.

## ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Modules I, II and VI.

## **6. Action ‘Clarifying requirements for reporting by the MAH of adverse reactions with compassionate use, named patient use or emergency use’**

### ***Problem statement***

- According to current legislation, EudraVigilance should be used to collate pharmacovigilance information regarding medicinal products authorised in the EU and to allow competent authorities to access that information simultaneously and to share it.<sup>11</sup> EudraVigilance shall contain information on suspected adverse reactions in human beings arising from the use of the medicinal product within the terms of the marketing authorisation as well as from uses outside the terms of the marketing authorisation, and on those occurring in the course of post-authorisation studies or associated with occupational exposure. These individual case safety reports (ICSRs) are submitted to the EudraVigilance Post-authorisation Module (EVP) by the MAH and competent authorities in Member States in accordance with the legal requirements.<sup>12</sup>

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<sup>11</sup> Article 24(1) par.1 of Regulation (EC) No 726/2004: “The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing network (hereinafter the ‘Eudravigilance database’) to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.”

<sup>12</sup> Article 107(3) of Directive 2001/83/EC: “Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the ‘Eudravigilance database’) information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.” and

Article 107a(4) of Directive 2001/83/EC: “Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database. They shall, within 90 days from the receipt

In line with Article 40 of Regulation (EU) No 536/2014, the EudraVigilance database also contains information on suspected unexpected serious adverse reactions (SUSARs) reported by sponsors of interventional clinical trials pursuant to Article 42 of that Regulation. These reports are submitted to the EudraVigilance Clinical Trial Module (EVCTM).<sup>13</sup>

- It is however considered that there is a gap in the legislation concerning the collection, management and submission to EudraVigilance of suspected adverse reaction cases by applicants/pharmaceutical companies and Member States for medicinal products distributed to patients in accordance with the provisions detailed in Articles 5(1) or 5(2) of Directive 2001/83/EC<sup>14</sup>, Article 5(3) of Regulation (EC) No 726/2004<sup>15</sup>, Article 83 of Regulation (EC) No 726/2004<sup>16</sup>, or otherwise distributed in Member States for these purposes within schemes based on national legislation, when no marketing authorisation has (yet) been granted in the EU for the concerned medicinal product, i.e. so-called compassionate use, named patient use or emergency use. In this context, there is a further gap in the legislation concerning the submission of medicinal product information to the eXtended EudraVigilance Medical Products Dictionary (XEVMPPD). These products may have ongoing clinical trials in parallel in the EU in multiple Member States and they may also be under rolling review for accelerated authorisation and/or under evaluation for a marketing authorisation. SUSARs submitted to EVCTM will be accessible to Member States to support cooperation in assessing the safety of active substances used in clinical trials, in line with Regulation (EU) No 536/2014. However, cases of suspected adverse reactions concerning the same active substances but occurring in the frame of the distribution of the products to patients under compassionate use, named patient use or emergency use may not be made available to all concerned Member States for safety monitoring cooperation since there is no EU regulatory requirement regarding the management and submission to EudraVigilance of pharmacovigilance information for these cases. In addition, where individual

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*of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database. Marketing authorisation holders shall access those reports through the Eudravigilance database.”*

<sup>13</sup> Article 40 of Regulation (EU) No 536/2014:

*“1. The European Medicines Agency established by Regulation (EC) No 726/2004 (the ‘Agency’) shall set up and maintain an electronic database for the reporting provided for in Articles 42 and 43. That database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004 (the ‘Eudravigilance database’).*

*2. The Agency shall, in collaboration with Member States, develop a standard web-based structured form for the reporting by sponsors to the database referred to in paragraph 1 of suspected unexpected serious adverse reactions.”* and

Article 42(1) of Regulation (EU) No 536/2014: *“The sponsor of a clinical trial performed in at least one Member State shall report electronically and without delay to the database referred to in Article 40(1) all relevant information about the following suspected unexpected serious adverse reactions: [...]”*

<sup>14</sup> Article 5(1) and (2) of Directive 2001/83/EC:

*“1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.*

*2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.”*

<sup>15</sup> Article 5(3) of Regulation (EC) No 726/2004: *“At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Human Use shall also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. The Committee shall take due account of any requests by Member States for an opinion. The Committee shall also formulate an opinion whenever there is disagreement in the evaluation of medicinal products through the mutual recognition procedure. The opinion of the Committee shall be made publicly accessible.”*

<sup>16</sup> Article 83 of Regulation (EC) No 726/2004:

*“1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.*

*2. For the purposes of this Article, ‘compassionate use’ shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.*

*[...]”*

Member States collect and submit these cases to EudraVigilance, there is no regulatory requirement allowing the applicant/pharmaceutical company to access these cases in EudraVigilance since the product is not (yet) authorised. The companies need to contact each national competent authority where their product is used under compassionate use, named patient use or emergency use to request copies of those ICSRs.

- Beyond constituting legal gaps, this carries an administrative burden for both pharmaceutical companies and national competent authorities, may lead to time delays in safety surveillance and hinders the cooperation for safety monitoring between the companies and Member States.

### ***Problem solution – Proposed legal intent***

- It is proposed to clarify the legal provisions and close the gaps for the applicant/pharmaceutical companies and Member States regarding the management of medicinal product information and pharmacovigilance information for medicinal products distributed to patients under compassionate use, named patient use or emergency use in accordance with the provisions detailed in Articles 5(1) or 5(2) of Directive 2001/83/EC, Article 83 of Regulation (EC) No 726/2004, based on a CHMP opinion adopted under Article 5(3) of Regulation (EC) No 726/2004 or otherwise distributed in Member States for these purposes within schemes based on national legislation. The clarifications should ensure:
  - the collection, management and submission of ICSRs in EudraVigilance;
  - the submission of medicinal product information to the the eXtended EudraVigilance Medical Products Dictionary (XEVMPPD); and
  - the support to national decision-making on existing or future marketing authorisations based on these data (proposed to amend Articles 5(1) and 5(2) of Directive 2001/83/EC and Articles 5(3) and 83 of Regulation (EC) No 726/2004).

### ***Problem solution – Proposed guidance***

The new legal provisions would be further detailed in GVP Module VI. Also, the EudraVigilance Access Policy would need to be amended to allow pharmaceutical companies to access, in EudraVigilance, ICSRs that are collected and submitted to EudraVigilance by Member States concerning their products distributed to patients under named patient use, compassionate use or emergency use.

## **7. Action ‘Requiring the applicant to enter data in XEVMPPD’**

### ***Problem statement***

- From the time of submission of a marketing application, the applicant has the obligation to submit to EudraVigilance post-marketing individual case safety reports (ICSRs) from third countries where the product is authorised.
- However, the legal obligation to enter the medicinal product applied for in the eXtended EudraVigilance Medical Products Dictionary (XEVMPPD) applies only to the marketing authorisation holder<sup>17</sup>; the applicant does not have such legal obligation.

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<sup>17</sup> Article 57(2)(c) of Regulation (EC) No 726/2004: “from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a).”

- This can lead to product-identifying information reported in ICSRs not being recoded, which in turn can hamper the identification of safety signals related to such products in EudraVigilance.

### ***Problem solution – Proposed legal intent***

- It is proposed to require the applicant to enter product data in XEVMPD at the time of application, by amending Article 57(2)(c) of Regulation (EC) No 726/2004 to include that the applicant shall inform EMA of any new applications for marketing authorisations requested in the EU, using the format referred to in point (a) of this Article (proposed to amend Article 57(2)(c) of Regulation (EC) No 726/2004).

### ***Problem solutions in guidance***

The new legal provisions would be further detailed in GVP Module VI.

## **8. Action 'Prohibiting resubmission of data downloaded from EudraVigilance to EudraVigilance'**

### ***Problem statement***

- MAHs are required to submit individual case safety reports (ICSRs) to EudraVigilance<sup>18</sup> and can obtain ICSRs from EudraVigilance in accordance with current legislation.<sup>19</sup>
- MAHs will often share this ICSR information with their commercial partners or will amend the information in their own databases, e.g. with the addition of assumed adverse reactions or results of batch testing. The amended ICSRs or ICSRs received from commercial partners with amendments are then often resubmitted to EudraVigilance, even though they contain no new information from the primary reporting source.
- This creates duplicate case reports in EudraVigilance, harming the ability of EMA and Member States to monitor the safety of medicinal products by impacting negatively on quantitative signal detection and delaying signal assessment. It requires a vast amount of resources for duplicate detection and cleaning before a proper ICSR evaluation for a specific signal can be performed. Removal of these duplicate case reports costs EMA significant sums of money (over €300,000 per annum) and constitutes a major workload. Duplicates also jeopardise providing correct numbers of adverse reaction cases to the public.

<sup>18</sup> Article 107(3) of Directive 2001/83/EC:

*"Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*

*Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*

*For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions."*

<sup>19</sup> Article 24(2) par. 5 of Regulation (EC) No 726/2004: *"The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations."*



### ***Problem solution – Proposed legal intent***

- It is proposed to include in the legislation an explicit statement that ICSRs which were obtained from EudraVigilance (either directly or indirectly via a commercial partner or another MAH) should not be re-submitted by the MAH to EudraVigilance, unless an ICSR has been amended to contain additional information received from the primary reporting source (proposed to amend Article 107(3) of Directive 2001/83/EC).

### ***Problem solutions in guidance***

The new legal provisions would be further detailed in GVP Module VI.

## **9. Action ‘Requiring contingency planning for when the MAH ceases to exist’**

### ***Problem statement***

- When a company or another legal entity that is MAH of a medicinal product ceases to exist (e.g. due to bankruptcy), or when the marketing authorisation is being revoked (e.g. because the MAH voluntarily withdraws the product from the market at their own decision and asks the competent authority to revoke the marketing authorisation) or, for nationally authorised products in some Member States, when the MAH sells the marketing authorisation to another legal entity, there is no legal requirement to continue fulfilling pharmacovigilance activities for the legal entity constituting the former MAH, and hence the data such former MAH holds might no longer be part of the existing legal requirements for record keeping.<sup>20</sup> Any obligation the former MAH may have had, such as the start of conducting post-authorisation safety studies (PASS) or continued dissemination of additional risk minimisation measures (RMM), might also remain unfulfilled.
- This might jeopardise, for concerned products (which may remain in distribution for a considerable amount of time), the identification of adverse reactions (e.g. with delayed onset or long-term impact) and the continuous implementation of RMM as well as advice to healthcare professionals and patients in an evidence-based manner.

### ***Problem solution – Proposed legal intent***

- When a nationally authorised product is sold to another legal entity, a legal requirement explicitly stating that all the responsibilities of the former MAH, including all pharmacovigilance obligations, are transferred to the buying legal entity is proposed (to be consistent with the provisions for the transfer of marketing authorisations in place for centrally authorised products<sup>21</sup>) (proposed to amend Article 104 of Directive 2001/83/EC).
- Regarding bankruptcy, it is proposed to introduce a provision requiring that, as part of the pharmacovigilance system, the MAH should set funds aside or take an insurance for situations

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<sup>20</sup> Article 12(2) of Commission Implementing Regulation (EU) No 520/2012: “Marketing authorisation holders shall arrange for the elements referred to in Article 2 to be kept for at least five years after the system as described in the pharmacovigilance system master file has been formally terminated by the marketing authorisation holder. Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires.”

<sup>21</sup> Commission Regulation (EC) No 2141/96 concerning the examination of an application for the transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93

necessitating handing over record keeping and, if applicable, oversight of PASS (studying previously exposed patients if the product has ceased to exist) or continued dissemination of additional RMM to another company that is notified to the competent authority and has power of attorney to respond to requests from the competent authority (including records held by the former MAH) and the obligation to submit committed data (proposed to amend Article 104 of Directive 2001/83/EC).

- Where the given new circumstances will result in the medicinal product remaining in distribution only for a limited amount of time, the competent authority should have the opportunity to waive the requirements regarding PASS if they consider that such studies are not risk-proportionate anymore.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Module I.

## **ACTION AREA B: Streamlining procedures for focus and efficiency of pharmacovigilance**

### **10. Action 'Clarifying the delegation of supervisory authority role to another Member State'**

#### ***Problem statement***

- Current legislation for human medicines allows competent authorities of Member States to delegate any of their tasks to another Member State<sup>22</sup>, without specifying that this legal provision includes pharmacovigilance inspections.
- However, Article 79 of Regulation (EU) 2019/6 for veterinary medicines mentions in this respect pharmacovigilance inspections specifically.
- Recognising that the human and veterinary regulations have been approved and reviewed at different timepoints, it is considered that there is an inconsistency between Article 19(1) of Regulation (EC) 726/2004<sup>23</sup> and Article 79 of Regulation (EU) 2019/6, which may now cause uncertainty.

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<sup>22</sup> Article 103 of Directive 2001/83/EC: "A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State. The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public."

<sup>23</sup> Article 19(1) of Regulation (EC) No 726/2004: "The supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product or the manufacturer or importer established within the Union satisfies the requirements concerning manufacturing and imports laid down in Titles IV and XI of Directive 2001/83/EC. The supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC. They may, if this is considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant in support of his application."

## **Problem solution – Proposed legal intent**

- It is proposed to amend the legislation for human medicines to explicitly include the option to delegate the role as a supervisory authority for pharmacovigilance and pharmacovigilance inspections to another Member State after written agreement between the involved parties (proposed to amend Article 19(1) of Regulation (EC) 726/2004).

## **Proposed solutions in guidance**

The new legal provisions would be further detailed in GVP Module III.

# **11. Action 'Replacing some of the adverse reaction reporting requirements for the MAH with data exchange agreements between EMA and non-EU regulatory authorities'**

## **Problem statement**

- The current legislation requires the MAH to record and report to EudraVigilance all suspected adverse reactions reported from Member States or third countries.<sup>24</sup> In accordance with these legal provisions and GVP Module VI, section VI.C.2.2, the MAH should also report if its ownership of the suspected product cannot be excluded on the basis of the medicinal product name, active substance name, pharmaceutical form, batch number or route of administration.
- Since a number of third country regulatory authorities (e.g. Australia, Canada, New Zealand) now publish electronically (or make otherwise available to MAHs) information on suspected adverse reactions, MAHs are becoming aware of adverse reaction cases for which they cannot exclude their product ownership. When multiple MAHs hold marketing authorisations for medicinal products containing the same active substance both in these countries and within the EU, they all have the same reporting requirement to the EU, which leads to the submission to EudraVigilance of the same individual case safety reports (ICSRs) multiple times.
- This creates a very large number of duplicate case reports in EudraVigilance, impacting negatively on quantitative signal detection and delaying signal assessment in the EU, as well as requiring a vast amount of resources for duplicate detection and cleaning before a proper ICSR evaluation for a specific signal can be performed. As a prominent example, ICSRs for COVID-19 vaccines had to be cleaned up within very short time frames and with urgent outreach to

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<sup>24</sup> Article 107(1)&(3) of Directive 2001/83/EC:

*"1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study. Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union. By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC. (...)*

*3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*

*Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*

*For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions."*

third countries, for avoiding delays in signal assessment and for providing correct numbers of adverse reaction cases to the public.

### ***Problem solution – Proposed legal intent***

- It is proposed to extend legal responsibilities of EMA to developing and implementing agreements for direct safety data exchange of information on suspected adverse reactions with third country regulatory authorities who are making them available to MAHs. The level of information shared should be done while respecting the EU data protection rules, in particular Regulation (EU) 2018/1725, i.e. the EU Data Protection Regulation (EU DPR), and Regulation (EU) 2016/6792, i.e. the General Data Protection Regulation (GDPR) (proposed to e.g. amend Article 28c(1) of Regulation (EC) 726/2004<sup>25</sup>).
- EMA should publish a list of countries and regulatory authorities concerned by these direct safety data exchange agreements for information on suspected adverse reactions (proposed to amend e.g. Article 28c(1) of Regulation (EC) 726/2004).
- The MAH should no longer be required to submit information on serious suspected adverse reactions it receives from third country regulatory authorities with whom EMA has set up direct safety data exchange agreements and which are detailed in the list maintained and published by EMA. For adverse reaction cases from those countries, the MAH should only submit to EudraVigilance within 15 days information on all serious suspected adverse reactions they receive directly from patients and healthcare professionals or occurring in the context of a post-authorisation study. The submission requirements to the EudraVigilance database for the MAH should remain unchanged for information on serious and non-serious adverse reactions occurring in the EU and for information from third country regulatory authorities that are not included in the list published by EMA (proposed to amend Article 107(3) of Directive 2001/83/EC).
- The legal requirements provided in Article 107(1) of Directive 2001/83/EC should *not* be amended and the MAH should continue recording all suspected adverse reactions in the EU or in third countries which are brought to its attention.

### ***Problem solution – Proposed guidance***

The new legal provisions would be further detailed in GVP Modules VI.

## **12. Action ‘Removing (or re-scoping) the additional monitoring status’**

### ***Problem statement***

- Current legislation requires additional monitoring for all medicinal products that contain a new active substance, are a new biological medicinal product or have been authorised with certain obligations and provides for optional allocation of additional monitoring status in other

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<sup>25</sup> Article 28c(1) of Regulation (EC) No 726/2004: “The Agency shall collaborate with the World Health Organisation in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Union which may have a bearing on public health protection in third countries.  
The Agency shall make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organisation.”

circumstances, also to already authorised products. EMA is required to publish a list of products under additional monitoring.<sup>26</sup>

- However, an evaluation conducted in accordance with the legislation of 2010<sup>27</sup> and published by the European Commission was inconclusive regarding the impact and added value of the additional monitoring status on increasing spontaneous reporting of adverse reactions and on signal detection.<sup>28</sup> The evaluation included an Italian study showing that underreporting of adverse reactions by physicians also involved medicinal products subject to additional monitoring<sup>29</sup>; an Irish study finding that among those healthcare professionals who knew about additional monitoring, awareness of the black triangle symbol was only high among pharmacists (> 86.4%) compared to hospital doctors (35.1%), general practitioners (35.6%) and nurses (14.9%)<sup>30</sup>; and a systematic review which identified that lack of knowledge, uncertainty about causality and indifferent attitude are the main roots for underreporting by healthcare professionals and called for educational and motivational intervention<sup>31</sup>. A systematic review identified lack of awareness and confusion who should report and to whom as barriers to reporting for patients.<sup>32</sup> It is considered that the statement “This medicinal product is subject to additional monitoring” in the package leaflet cannot improve this.
- Since this evaluation, newer research by EMA published in 2021 on the understanding and behavioural impact of the additional monitoring symbol found it also difficult to conclude whether the symbol had an effect on spontaneous reporting and questioned if wide awareness campaigns on the additional monitoring are an efficient use of resource, given that many patients and healthcare professionals might not even encounter a medicine with the additional monitoring status.<sup>33</sup> Further EMA research published in 2021 identified only limited evidence

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<sup>26</sup> Article 23 of Regulation (EC) No 726/2004:

“1. The Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring. That list shall include the names and active substances of:

(a) medicinal products authorised in the Union that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the Union;

(b) any biological medicinal product not covered by point (a) that was authorised after 1 January 2011;

(c) medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in point (cb) of Article 9(4), point (a) of the first subparagraph of Article 10a(1) or Article 14(7) or (8);

(d) medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (b) and (c) of the first paragraph of Article 21a, Article 22, or point (a) of the first subparagraph of Article 22a(1) thereof.

1a. At the request of the Commission, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in points (c), (ca) or (cc) of Article 9(4), point (b) of the first subparagraph of Article 10a(1) or Article 21(2), may also be included in the list referred to in paragraph 1 of this Article.

At the request of a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (a), (d), (e) or (f) of the first paragraph of Article 21a, point (b) of the first subparagraph of Article 22a(1) or Article 104a(2) thereof, may also be included in the list referred to in paragraph 1 of this Article.

[...]

4. For medicinal products included in the list referred to in paragraph 1, the summary of product characteristics and the package leaflet shall include the statement ‘This medicinal product is subject to additional monitoring’. That statement shall be preceded by a black symbol which shall be selected by the Commission by 2 July 2013, following a recommendation of the Pharmacovigilance Risk Assessment Committee, and shall be followed by an appropriate standardised explanatory sentence. [...]”

<sup>27</sup> Article 23(4a) of Regulation (EC) No 726/2004: “By 5 June 2018, the Commission shall present to the European Parliament and the Council a report on the use of the list referred to in paragraph 1 based on the experience and data provided by the Member States and the Agency.”

<sup>28</sup> Report from the Commission to the European Parliament and the Council on the National and European Medicines Agency experience regarding the list of medicines for human use subject to additional monitoring; 15 November 2019. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2019:591:FIN>.

<sup>29</sup> Patrignani A, Palmieri G, Ciampani N, Moretti V, Mariani A, Racca L. Under-reporting of adverse drug reactions, a problem that also involves medicines subject to additional monitoring. Preliminary data from a single-center experience on novel oral anticoagulants. *G Ital Cardiol*. 2018; 19: 54-61.

<sup>30</sup> O’Callaghan J et al. Knowledge of adverse drug reaction reporting and the pharmacovigilance of biological medicines: a survey of healthcare professionals in Ireland. *Bio Drugs*. 2018; 32:267-280.

<sup>31</sup> Varallo FR, Guimaraes SOP, Abjaude SAR, Mastroianni PC. Causes for the underreporting of adverse drug events by health professionals: a systematic review. *Rev Esc Enferm USP*. 2014; 48: 739-747.

<sup>32</sup> Al Dweik R et al. Factors affecting patient reporting of adverse drug reactions: a systematic review. *Br J Clin Pharmacol*. 2017; 83: 875-883.

<sup>33</sup> Januskiene, J, Segec, A, Slattery, J, et al. What are the patients' and health care professionals' understanding and behaviors towards adverse drug reaction reporting and additional monitoring? *Pharmacoepidemiol Drug Saf*. 2021; 30: 334-341. DOI: 10.1002/pds.5162.

that spontaneous reporting increased modestly and gradually for some new products due to their additional monitoring status.<sup>34</sup> Research in Australia on their black triangle scheme also showed only marginal success in improving spontaneous reporting.<sup>35</sup>

- As the additional monitoring status has not resulted in the expected higher spontaneous reporting of suspected adverse reactions in the EU, the related requirements for both the MAHs and the EU regulatory network are considered an unnecessary burden and pharmacovigilance resources might be more efficiently used in other initiatives to improve spontaneous reporting.

### **Proposed legal intent for problem resolution**

- It is proposed to remove the legal provisions relating to additional monitoring (proposed to delete Article 23 of Regulation (EC) 726/2004 and to amend Articles 11, 59 and 106 of Directive 2001/83/EC) (alternatively, the scope of the additional monitoring status could be revised).

### **Proposed solutions in guidance**

GVP Module X and any references to additional monitoring in other GVP documents would be removed (or revised) in accordance with this amendment of the legislation.

## **13. Action 'Removing the marketing authorisation renewal'**

### **Problem statement**

- The current legislation requires a renewal of the marketing authorisation after five years of granting the marketing authorisation for all medicinal products.<sup>36</sup>

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<sup>34</sup> Segec, A, Slattery, J, Morales, DR, Januskiene, J, Kurz, X, Arlett, P. Does additional monitoring status increase the reporting of adverse drug reactions? An interrupted time series analysis of EudraVigilance data. *Pharmacoepidemiol Drug Saf.* 2021; 30: 350-359. DOI: 10.1002/pds.5174

<sup>35</sup> R, Curtis K, Zaidi STR, Van C, Castelino R. Effect of the black triangle scheme and its online educational campaign on the quantity and quality of adverse drug event reporting in Australia: a time series analysis. *Expert Opin Drug Saf.* 2020;19: 747-753. DOI: 10.1080/14740338.2020.1746762.

<sup>36</sup> Article 24 of Directive 2001/83/EC:

*"1. Without prejudice to paragraphs 4 and 5, a marketing authorisation shall be valid for five years.*

*2. The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.*

*To this end, the marketing authorisation holder shall provide the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with paragraph 1.*

*3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.*

*4. Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.*

*5. When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.*

*6. The competent authority may, in exceptional circumstances and on public health grounds grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified."* and

Article 14(1-2) of Regulation (EC) No 726/2004:

*"1. Without prejudice to paragraphs 4 and 5 of this Article and to Article 14-a, a marketing authorisation shall be valid for five years.*

*2. The marketing authorisation may be renewed after five years on the basis of a re-evaluation by the Agency of the risk-benefit balance. To this end, the marketing authorisation holder shall provide the Agency with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Chapter 3, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with paragraph 1."*

- However, renewals have very seldomly resulted in a product withdrawal or amendments to the conditions for marketing authorisation, and experience at PRAC has shown that the renewal procedure does not add value with regard to safety, given the assessment of periodic safety update reports (PSURs) that cover accumulating safety data and their impact on the known risk-benefit balance in the prescribed ICH format and contents of the periodic benefit-risk evaluation report (PBRER).<sup>37</sup>
- From a safety perspective, the renewal procedure is hence considered an unnecessary burden.

### **Problem solution – Proposed legal intent**

- From a safety perspective, considering that safety data are assessed in PSURs, it is proposed - within this Concept Paper on the legal provisions for pharmacovigilance - to remove the legal requirement for renewals of the marketing authorisation (proposed to amend Article 24 Directive 2001/83/EC and Article 14 of Regulation (EC) 726/2004).
- It is acknowledged that removing the renewal procedure would require assessing efficacy data through other existing applicable regulatory procedures, such as post-authorisation measure (PAM), legally binding procedure (LEG) relying on Article 16 of Regulation (EC) No 726/2004<sup>38</sup>, variation or referral procedures. Further, it is acknowledged that the regulatory oversight of the risk-benefit balance and the regulatory accountability needs to remain explicit and visible within the regulatory system and as well as externally.
- Applying existing procedures for efficacy data alongside the PSUR procedure allows for a near-time benefit-risk management of medicinal products as evidence is accumulating, without being bound to a predefined renewal schedule.

### **Proposed solutions in guidance**

The section on renewals in the post-authorisation guidance would have to be deleted, and likewise any reference to renewals in GVP.

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<sup>37</sup> Article 107b(1) of Directive 2001/83/EC: "Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(b) a scientific evaluation of the risk-benefit balance of the medicinal product;

[...]" and

Article 34 of Commission Implementing Regulation (EU) No 520/2012

<sup>38</sup> Article 16 of Regulation (EC) No 726/2004:

"1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of corresponding variations in accordance with this Regulation.

2. The marketing authorisation holder shall forthwith provide the Agency, the Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Article 10, 10a, 10b and 11, or Article 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, the marketing authorisation holder shall forthwith inform the Agency and the Commission of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26.

3a. In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest seven days after receipt of the request."

## 14. Action 'Relying on PSURs for the annual re-assessment and the annual renewal'

### **Problem statement**

- The current legislation requires an annual reassessment for medicinal products authorised under exceptional circumstances<sup>39</sup> and an annual renewal for medicinal products with a conditional marketing authorisation.<sup>40</sup>
- However, experience at PRAC has shown that these procedures do not add value with regard to safety, given that risk assessments are performed regularly through the framework for periodic safety assessment reports (PSURs), which cover accumulating safety data and their impact on the known risk-benefit balance in the prescribed ICH format and contents of the periodic benefit-risk evaluation report (PBRER).<sup>41</sup>
- From a safety perspective, both the annual re-assessment and the annual renewal procedures are hence considered an unnecessary burden, given that the EU regulatory pharmacovigilance system provides for continuous processes of safety surveillance and risk management. It is noted that for the annual renewal efficacy aspects can be subject to the specific obligation (SOB) and variation (VAR) procedures, and the PSURs can be an effective way to track progress with safety-related SOBs every 6 months. It is also noted that for the annual re-assessment only few patients will be in registries and efficacy data will be submitted in the PSURs and can be requested and assessed via a VAR Type II procedure.
- It is furthermore noted that current legislation prescribes that PSURs for medicinal products subject to conditional marketing authorisations have to be provided at least every 6 months.<sup>42</sup> As sometimes the safety profile of a medicinal product stabilises before final clinical data on efficacy can be provided by the MAH, it would be desirable that PRAC has the option to request PSUR schedules relevant to the established safety profile and in risk-proportionate manner, which could be less frequent than every 6 months. This is particularly relevant for products that remain under conditional marketing authorisation from more than 2 years.

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<sup>39</sup>Article 22 of Directive 2001/83/EC:

*"In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.*

*The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.*

*Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions."* and

Article 14(8) of Regulation (EC) No 726/2004: *"In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions."*

<sup>40</sup> Article 14a(7) of Regulation (EC) No 726/2004: *"By way of derogation from Article 14(1), a marketing authorisation granted pursuant to this Article shall be valid for one year, on a renewable basis."*

<sup>41</sup> Article 107b(1) of Directive 2001/83/EC: *"Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:*

*(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;*

*(b) a scientific evaluation of the risk-benefit balance of the medicinal product;*

*[...]"* and

Article 34 of Commission Implementing Regulation (EU) No 520/2012

<sup>42</sup> Article 9 of Commission Regulation (EC) No 507/2006: *"The periodic safety update reports provided for in Article 24(3) of Regulation (EC) No 726/2004 shall be submitted to the Agency and Member States immediately upon request or at least every six months following the granting or renewal of a conditional marketing authorisation."*



### ***Problem solution – Proposed legal intent***

- It is proposed that to the annual re-assessment and annual renewal procedures rely on PSURs by means of legal provisions, in a way that avoids duplication of safety assessments for annual re-assessments/annual renewals (proposed to amend Article 22 Directive 2001/83/EC and Articles 14(7) and 14(8) of Regulation (EC) No 726/2004).
- It is further proposed to legally allow PRAC to determine risk-proportionate PSUR schedules for medicinal products subject to conditional marketing authorisations (proposed to amend Article 9 of Commission Regulation (EC) No 507/2006).

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in the post-authorisation guidance and GVP Module VII.

## **15. Action ‘Removing RMPs for generic, biosimilar, hybrid and informed consent products where the reference product does not have an aRMM, unless requested)’**

### ***Problem statement***

- The current legal requirement for risk management plans (RMPs) applies to all new marketing authorisation applications, including those for generic, biosimilar, hybrid and informed consent products.<sup>43</sup>
- However, for generic, biosimilar, hybrid and informed consent products whose reference product does not have any additional risk minimisation measure (aRMM) in the RMP, this is considered a burden for MAHs and the EU regulatory network without an added value for patient safety.

### ***Problem solution – Proposed legal intent***

- It is proposed that for generic, biosimilar, hybrid and informed consent products a RMP is only required if the reference product has an aRMM. In the case that the reference product has no aRMM, PRAC or the national competent authority should be able to request a RMP from the MAH at any time based on pharmacovigilance grounds (proposed to amend Annex I of Directive 2001/83/EC).
- When a aRMM is newly required for the originator product during the post-authorisation phase, the MAHs for the generic, biosimilar, hybrid or informed consent product would have to submit an aligned RMP too, and where the originator product has ceased or ceases to exist, this new RMP would have to be established by the MAHs for the generic, biosimilar, hybrid or informed consent products.

### ***Proposed solutions in guidance***

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<sup>43</sup> Article 8(3)(iaa) of Directive 2001/83/EC: [“The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I”:] “The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.”

These new legal provisions would be further detailed in GVP Module V. To support efficiency, a policy of the EU regulatory network for web-publication of RMP would be developed.

## **16. Action 'Replacing the default PSUR schedule with risk-based schedules for nationally authorised products not in the EURD list'**

### ***Problem statement***

- Current legislation requires the submission of periodic safety update reports (PSURs) according to a defined default schedule for all medicinal products<sup>44</sup> authorised in the EU or any Member State before July 2012<sup>45</sup>. For products with the same active substance, the list of European Union reference dates and frequency of submission of PSURs (EURD List)<sup>46</sup> facilitates the EU single assessment process of PSURs<sup>47</sup> with schedules determined in a risk-proportionate manner (i.e. different from the default PSUR schedule).
- Products only authorised in one Member State or for which there is no EU interest for a single PSUR assessment are not part of the EURD list and the default PSUR schedule applies (unless other dates of submission are laid down as a condition to the marketing authorisation). As a result, products with long experience of safe use are also subject to a PSUR procedure every 3 years. While Member States have the opportunity to amend the default schedule, in practice the legal requirement for this to be done as a condition to the marketing authorisation adds administrative burden and results in a large number of products still subject to a PSUR procedure every 3 years.
- 3-yearly PSURs for products with long experience of safe use are considered to be not risk-proportionate and to constitute an unnecessary burden for MAHs and competent authorities.

### ***Problem solution – Proposed legal intent***

- It is proposed that the legislation specifies that for nationally authorised products authorised before July 2012, if the product is not on the EURD List, the 3-years PSUR procedure will apply, unless the national competent authority notifies the MAH of a different PSUR schedule. This notification may take any format, as defined nationally (proposed to amend Article 107c(2) of Directive 2001/83/EC).
- As the marketing authorisations for these products often do not have an Annex 2 or equivalent for describing the conditions of the marketing authorisation, the current legal provision should not include any longer the specification "as conditions of the marketing authorisation"<sup>48</sup>

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<sup>44</sup> Article 107b(1) of Directive 2001/83/EC: "Marketing authorisation holders shall submit to the Agency periodic safety update reports [...]" and Article 107c(2), 2nd paragraph: "Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

(a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter."

<sup>45</sup> Article 107c(2) of Directive 2001/83/EC and Article 28(2) Regulation (EC) No 726/2004

<sup>46</sup> Article 107c(7) of Directive 2001/83/EC

<sup>47</sup> Article 107c(4) of Directive 2001/83/EC

<sup>48</sup> Article 107c(2) par. 1 of Directive 2001/83/EC: "Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6."

currently prescribed by legislation when Member States want to amend the PSUR schedule (proposed to amend Article 107c(2) par. 1 of Directive 2001/83/EC).

### ***Proposed solutions in guidance***

These new legal provisions would be further detailed in GVP Module VII.

## **17. Action 'Reducing the time period when a change of the PSUR schedule in the EURD List takes effect'**

### ***Problem statement***

- Current legislation states that a change to the frequency and dates of submission of periodic safety update reports (PSURs) of medicinal products included in the list of European Union reference dates and frequency of submission of PSURs (EURD List) takes effect 6 months after the date of the publication of the revised EURD List<sup>49</sup>.
- In practice this means that changes to the EURD List have in some cases led to delay of implementing revised PSUR schedules, e.g. when higher PSUR frequencies were required for safety reasons or when less frequent PSURs would have been risk-proportionate.

### ***Problem solution – Proposed legal intent***

- It is proposed to legally reduce the time period when a change in the PSUR frequency and submission schedule in the EURD List takes effect from 6 to 4 months, which would avoid unnecessary delays in applying the new PSUR schedule, while still allowing sufficient PSUR preparation time for MAHs in the case of changes to earlier submission dates (proposed to amend Article 107c(7) of Directive 2001/83/EC).

### ***Proposed solutions in guidance***

These new legal provisions would be further detailed in GVP Module VII.

## **18. Action 'Simplifying PRAC requests and MAH submissions for additional data'**

### ***Problem statement***

- In accordance with the Quality of Opinion project initiated by the European Commission around 2012, all post-authorisation measures (PAM) have to be based within a clear legal framework, to ensure enforceability. This means that PRAC requests for additional data or studies from MAHs to further elucidate a safety concern have to fit into the available legal categories, i.e. legally binding procedure (LEG) relying on Article 16 of Regulation (EC) No 726/2004<sup>50</sup>,

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<sup>49</sup> Article 107c(7) of Directive 2001/83/EC: "The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal. Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect 6 months after the date of such publication."

<sup>50</sup> Article 16 of Regulation (EC) No 726/2004:

additional pharmacovigilance activity in the risk management plan (RMP) (MEA) formalised in the pharmacovigilance plan of the RMP<sup>51</sup>, specific obligation (SOB) for products authorised under exceptional circumstances, or other Annex II condition (ANX), or variation (VAR). Processes for the follow-up to periodic safety update reports (PSUFU) are also in place, as well as for recommendations for further development of the medicinal product (REC) for which information can be submitted as a PAM; however if data obtained in the framework of a REC have an impact on the authorised medicinal product and its product information, the MAH has the obligation to submit a VAR. VARs may also be applicable to other processes above.

- Given the above, the applicable categories need to be carefully considered by PRAC at each occasion of requesting data or a study, and each of the regulatory procedure has different rules, timetables, fees, etc. Furthermore, not all the submitted data in different procedures are easily retrievable for the EU regulatory network.
- It is considered that this complexity requires resources unnecessarily, both at the level of the EU regulatory network and the MAHs. The need to always link back to either of these procedural frameworks is very cumbersome, hence the proposal below emerges to empower PRAC to request data and studies without the need to reference back to any of these cumbersome provisions.

### ***Problem solution – Proposed legal intent***

- It is proposed that the legislation provides a single data request framework for PRAC and simplifies post-authorisation submissions of requested data as a variation (or an alternative single process), applicable to both centrally and nationally authorised products (proposed to add a new legal provision in Regulation (EC) No 726/2004, e.g. as a new Article 62a).
- Furthermore, it should be specified that all data submitted by MAHs in follow-up of the PRAC procedure for a periodic safety update report (PSUR) (e.g. PSUFU, LEG) have to be available in the PSUR repository as a single repository for the requested data (apart from those data that are part of the eCTD record keeping or included in the EU PAS Register) (proposed to amend Article 25a of Regulation (EC) No 726/2004<sup>52</sup>).

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*“1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of corresponding variations in accordance with this Regulation.*

*2. The marketing authorisation holder shall forthwith provide the Agency, the Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Article 10, 10a, 10b and 11, or Article 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.*

*In particular, the marketing authorisation holder shall forthwith inform the Agency and the Commission of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.*

*3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26.*

*3a. In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.*

*The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest seven days after receipt of the request.”*

<sup>51</sup> Article 8(3)(1aa) of Directive 2001/83/EC: “The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I: [...] The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.”

<sup>52</sup> Article 25a, par 1 of Regulation (EC) No 726/2004: “The Agency shall, in collaboration with the national competent authorities and the Commission, set up and maintain a repository for periodic safety update reports (hereinafter the ‘repository’) and the corresponding assessment

- The simplified data submission process should also be applied to the submission of post-authorisation study documents, in particular for imposed post-authorisation safety study (PASS) protocols, protocol amendments and results (proposed to amend Article 107m of Directive 2001/83/EC).

### ***Proposed solutions in guidance***

These new legal provisions would be further detailed in the post-authorisation guidance and the GVP Modules VII and VIII.

## **19. Action 'Requiring MAHs to conduct joint PASS'**

### ***Problem statement***

- Current legislation provides for requesting post-authorisation safety studies (PASS) from the MAH and requires EMA or the national competent authority to encourage MAHs to conduct a joint PASS if a safety concern applies to more than one medicinal product<sup>53</sup>.
- However, practice has shown that the current framework does not result in satisfactory voluntary collaboration of MAHs.
- This is considered to be of major disadvantage, as joint PASS would cover wider EU populations, benefit from sharing methodological knowledge and deliver PASS results that would allow for identifying differential risks and related risk-proportionate and consistent action.

### ***Problem solution – Proposed legal intent***

- It is proposed that the European Commission considers how future legislation could possibly make collaboration of MAHs for joint PASS a more mandatory element, also allowing, in duly justified circumstances, not to have to engage in such collaboration (proposed to amend e.g. Article 22a(1)(a) of Directive 2001/83/EC and Article 10a(1)(a) of Regulation (EC) No 726/2004).

### ***Proposed solutions in guidance***

These new legal provisions would be further detailed in GVP Module VIII, and maybe also in Modules V and XVI.

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reports so that they are fully and permanently accessible to the Commission, the national competent authorities, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter the 'coordination group').

<sup>53</sup> Article 22a(1)(a) of Directive 2001/83/EC: "After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study" and

Article 10a(1)(a) of Regulation (EC) No 726/2004 "After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study."

## 20. Action 'Requiring registration of Category 3 PASS in the EU PAS Register'

### **Problem statement**

- For non-interventional post-authorisation safety studies (PASS) conducted pursuant to an obligation of the marketing authorisation (i.e. Category 1 and 2 PASS), the legislation requires the MAH to register the studies in the public EU PAS Register<sup>54</sup>, while it does not so for PASS belonging to Category 3.
- However, Category 3 PASS are equally included in the risk management plan (RMP) and legally enforceable, and the majority of PASS in RMPs belong to Category 3 and their registration is already mandatory in a number of Member States.
- Mandatory registration of all PASS included in RMPs is considered important to support transparency and facilitate the exchange of pharmacovigilance information between EMA, national competent authorities and MAHs. The recent scoping for revising the Commission Implementing Regulation (EU) No 520/2012 could not address this, because Directive 2001/83/EC does not provide for such legal requirement.

### **Problem solution – Proposed legal intent**

- It is proposed that registration, by the MAH, in the public register (i.e. the EU PAS Register) of all PASS in the RMP, including Category 3 PASS, is legally required (proposed to amend Article 107m(1) of Directive 2001/83/EC<sup>55</sup>) (see also Concept Paper 8).
- In this context, it is also suggested that post-authorisation efficacy studies (PAES) should be able to be classified as Category 3 studies.

### **Proposed solutions in guidance**

These new legal provisions would be further detailed in GVP Module VIII.

## 21. Action 'Reducing duplication of work between EMA committees'

### **Problem statement**

- It is considered that the current legal provisions<sup>56</sup> duplicate some work between committees, accompanied with a high administrative burden and the risk for some delay in initiating product information updates.

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<sup>54</sup> Commission Implementing Regulation (EU) No 520/2012 Annex III

<sup>55</sup> Article 107m(1) of Directive 2001/83/EC: "This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals."

<sup>56</sup> Article 56(1)(aa) of Regulation (EC) No 726/2004: "the Pharmacovigilance Risk Assessment Committee, which shall be responsible for providing recommendations to the Committee for Medicinal Products for Human Use and the coordination group on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems and it shall be responsible for monitoring the effectiveness of those risk management systems."

- This regularly duplicated workload is weighted against the very rare occurrences, over 10 years of PRAC operations, of differences in outcomes between committees, e.g. in signal and periodic safety update report (PSUR) assessments. Differences occurred more often regarding referral procedures.

### ***Problem solution – Proposed legal intent***

- The opportunity of this Concept Paper is taken to bring this to the attention of the European Commission and maybe the European Commission would want to consider some simplifications, e.g. demanding for centrally authorised products that only PRAC recommendations based on (a) divergent position(s) or for a restriction of indication or a product suspension/withdrawal are referred, avoiding duplication of assessments between PRAC, CHMP and/or CAT, or that PRAC recommendations for updates of the safety sections of product information resulting from PSUR assessments or from other regulatory pharmacovigilance procedures, e.g. signal assessments, become legally binding without CHMP or CMD(h) endorsement.
- However, the current procedure for referrals<sup>57</sup> involving PRAC as well as other committees should remain as is.

### ***Proposed solutions in guidance***

The Rules of Procedure of the respective committees would have to be amended and this would be further detailed in GVP Module I, and possibly in the EU network-specific C-sections of other Modules on specific pharmacovigilance processes.

## **22. Action ‘Considering pharmacovigilance fees for signals and Category 3 PASS’**

### ***Problem statement***

- Currently, no fees are applicable to assessments for signals as well as Category 3 post-authorisation safety study protocol and report review.
- As these assessments constitute a major workload, it is considered that the absence of fees for these activities make their inclusion in budget and resource plans of national competent authorities difficult.

### ***Problem solution – Proposed legal intent***

- As fees seem outside the scope of the current revision of legislation, no proposal is made in this Concept Paper, but the opportunity is taken to bring this to the attention of the European Commission for information and consideration.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in the applicable guidance as needed.

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<sup>57</sup> Article 31 of Directive 2001/83/EC, Article 107i of Directive 2001/83/EC and Article 20 of Regulation (EC) 726/2004

## 23. Action 'Providing a flexible safety procedure for product classes'

### ***Problem statement***

- Current procedures can assess safety concerns for multiple products with the same active substance or belonging to the same chemical and/or therapeutic class.<sup>58</sup>
- It is considered that the available procedures, where they are applied to cover multiple medicinal products and MAHs, are a major undertaking for the EU regulatory network, also from an administrative point of view, and hence constitute a high burden on the EU regulatory network with potential for delays in achieving consistent safety information in SmPCs/PLs and consistent risk minimisation measures (RMM) across products.

### ***Proposed legal intent for problem resolution***

- This is brought to the attention of the European Commission to maybe explore options for providing a more flexible way than the current procedures with regard to scope and timing, in order to achieve consistent safety information in SmPCs/PLs and consistent RMM (incl. RMM removal when they are not needed anymore) across medicinal products in an efficient manner (this could at least be appropriate where part of the assessment has already been performed in the context of another procedure, e.g. signal or periodic safety update report (PSUR) assessment).

### ***Problem solution – Proposed legal intent***

The new legal provisions would be further detailed in the post-authorisation guidance.

## ACTION AREA C: Enhancing effectiveness of safety-related actions for patient and public health

## 24. Action 'Requiring EU exposure data in PSURs'

### ***Problem statement***

- Current legislation requires the MAH to include in periodic safety update reports (PSURs) all data relating to the volume of sales of the medicinal product and any data in possession of the MAH relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.<sup>59</sup> Legislation also requires an accurate estimate of the exposed population, including all data relating to the volume of sales and volume of prescriptions, accompanied by a qualitative and quantitative analysis of actual use, which shall indicate,

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<sup>58</sup> Article 31 of Directive 2001/83/EC, Article 107i of Directive 2001/83/EC and Article 20 of Regulation (EC) 726/2004

<sup>59</sup> Article 107b(1)(c) of Directive 2001/83/EC: "Marketing authorisation holders shall submit to the Agency periodic safety update reports containing: [...] (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product."



where appropriate, how actual use differs from the indicated use based on all data available to the MAH, including the results of observational or drug utilisation studies.<sup>60</sup>

- However, no legal requirement exists to estimate or characterise the exposure in the EU, and less than half of submitted PSURs contain EU data, as a recent review at EMA has shown. Not only is the EU exposure poorly quantified, but also exposed populations are poorly described by age, sex, or other relevant characteristics.
- It is considered important that EU exposure data are available to the EU regulatory network as a denominator for analysing adverse reaction reporting data in EudraVigilance and for assessing risks as well as the public health impact of a safety concern and regulatory action in the EU.

### ***Problem solution – Proposed legal intent***

- It is proposed to legally require the MAH to provide data on sales of the medicinal product in the EU as well as any data in its possession relating to the EU prescription volume, including an estimate of the population exposed in the EU and qualitative and quantitative analyses of actual use in the EU, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the MAH, including the results of observational or medicines utilisation studies (proposed to amend Article 107b(1)(c) of Directive 2001/83/EC).
- This additional legal provision is not meant to replace the existing legal requirements resulting in the submission of worldwide exposure data as part of the PSURs as global documents and as data equally important for safety monitoring and risk assessment by the EU regulatory network based on worldwide data.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Module VII as a PSUR content item in the PSUR EU regional appendix, and possibly also in Module XVI.

## **25. Action 'Requiring RMM implementation status updates in PSURs'**

### ***Problem statement***

- Current legislation requires the EU regulatory network to monitor the outcome of risk minimisation measures (RMM).<sup>61</sup> Likewise, MAHs are required to monitor the outcome of RMM,

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<sup>60</sup> Article 34(2) of Commission Implementing Regulation (EU) No 520/2012: "The periodic safety update report shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorisation holder, including the results of observational or drug utilisation studies"

<sup>61</sup> Article 107h(1) of Directive 2001/83/EC: "Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures: (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a;" and Article 28c(1): "Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures: (a) monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8);"

and the RMP may require them to conduct studies to evaluate the effectiveness of RMM.<sup>62</sup>

- However, experience at PRAC has shown that the study results often take a long time to become available and there are no legal requirements for the MAH that enable any RMM monitoring by the EU regulatory network during this time period.
- It is considered a gap in the legislation that there is no requirement of monitoring that RMM are disseminated by MAHs to patients and healthcare professionals within the timeframes defined when the RMM are agreed, in particular additional RMM (aRMM). As a prominent example, the aRMM imposed on valproate-containing medicines by means of a referral in 2014 (educational materials) had not been disseminated fully by 2017, requiring a new referral procedure. Patient and healthcare representatives at the public hearing for this procedure in 2017 asked the EU regulatory network to monitor implementation of RMM in real time.<sup>63</sup>

### **Problem solution – Proposed legal intent**

- It is proposed to legally require the MAH to report the implementation status of RMM regularly in the periodic safety update reports (PSURs), including the launch of aRMM (i.e. the dates of disseminating aRMM to healthcare systems for the first time) in all Member States with reference to the dissemination timeframes defined when the aRMM have been agreed, and including the dissemination plans for sustainable implementation of aRMM (proposed to amend Article 107b(1) of Directive 2001/83/EC<sup>64</sup>).
- In addition, MAHs should be explicitly legally obliged to respond to ad hoc requests from PRAC or Member States regarding the implementation status of RMM (proposed to amend Article 23(4) par. 1 of Directive 2001/83/EC<sup>65</sup> and 16(3a) of Regulation (EC) No 726/2004<sup>66</sup>).

### **Proposed solutions in guidance**

The new legal provisions would be further detailed in GVP Modules VII and XVI.

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<sup>62</sup> Article 104(3)(d) of Directive 2001/83/EC: “As part of the pharmacovigilance system, the marketing authorisation holder shall: [...] monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a”

<sup>63</sup> Bahri P, Morales DR, A Inoubli, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel Analysing Stakeholder Safety Engagement Tool (ASSET). *Drug Saf. 2021; 44: 193–209* (epub 30 Oct 2020) doi: 10.1007/s40264-020-01005-3.

<sup>64</sup> Article 107b(1) of Directive 2001/83/EC: “Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(b) a scientific evaluation of the risk-benefit balance of the medicinal product;

(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

The periodic safety update reports shall be submitted electronically.”

<sup>65</sup> Article 23(4) par. 1 of Directive 2001/83/EC: “In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.”

<sup>66</sup> Article 16(3a) of Regulation (EC) No 726/2004: “3a. In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.”

## 26. Action 'Strengthening the legal basis for PPPs'

### ***Problem statement***

- Pregnancy prevention programmes (PPPs) are specific risk minimisation measures (RMM) for medicinal products with teratogenic potential to harm children exposed in utero.
- Guidance on determining if a PPP or other pregnancy-specific RMM are warranted for a given medicinal product has recently been developed as an Addendum to GVP Module XVI.<sup>67</sup>
- This GVP guidance consolidates current regulatory practice (i.e. PPPs already required for existing products) for a consistent application of RMM across teratogenic products; however, the European Commission, in their recent review of this draft GVP guidance, provided a comment regarding the legal basis of PPP elements. This concerns in particular the text via a visual reminder on the outer package to warn patient about the harm to the unborn baby and the need for effective contraception when using the medicinal product, which has been required for valproate<sup>68</sup> following a strong call from patient representatives during the public hearing for the valproate referral procedure.<sup>69</sup>

### ***Problem solution – Proposed legal intent***

- It is proposed that the European Commission investigates if the current legal basis for warranting a PPP or elements of it is possibly too weak and if strengthening of the legislation is required for warranting all PPP elements in the future, including a visual reminder on the outer package.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Module XVI and its Addendum on PPPs.

## 27. Action 'Requiring stakeholder consultations of aRMM'

### ***Problem statement***

- Current legislation requires MAHs to consult patients on package leaflets to ensure that they are legible, clear and easy to use<sup>70</sup>, known as readability testing further described in European Commission guidance.<sup>71</sup> This supports the legal requirements for the package leaflet itself to be written and designed in such a way as to be clear and understandable, enabling users to act appropriately.<sup>72</sup>

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<sup>67</sup> Release for public consultation scheduled for February or March 2022 accessible at: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices>.

<sup>68</sup> [https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iv\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iv_en.pdf).

<sup>69</sup> [https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy\\_en.pdf](https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf).

<sup>70</sup> Article 59(3) of Directive 2001/83/EC: "The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use."

<sup>71</sup> European Commission Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use; [https://ec.europa.eu/health/system/files/2016-11/2009\\_01\\_12\\_readability\\_guideline\\_final\\_en\\_0.pdf](https://ec.europa.eu/health/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf).

<sup>72</sup> Article 63(2) of Directive 2001/83/EC: "The package leaflet must be written and designed in such a way as to be clear and understandable, enabling users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State."

- As aRMM evaluations have shown that some additional risk minimisation measures (aRMM) are of unsatisfactory effectiveness<sup>73</sup>, a recent revision of GVP Module XVI recommends – in analogy to the package leaflet – user-testing of aRMM materials in the languages of Member States<sup>74</sup> to improve the impact of aRMM on patient and public health. This user-testing is meant to include usability of aRMM in given healthcare systems as a crucial prerequisite of aRMM effectiveness. In practice, a user testing was requested e.g. for the visual reminder of the teratogenic warning as an element of the pregnancy prevention programme for valproate, with the details of the visual reminder to be agreed at Member States' level and be subject to a user-test taking into account input from local patient representatives.<sup>75</sup>
- However, there is no legal requirement for comprehensive and purposeful stakeholder consultations of aRMM materials which are considered necessary to ensure readability, usability in healthcare systems and effectiveness of aRMM targeted at patients and healthcare professionals, given the crucial role of aRMM in maintaining the positive risk-benefit balance of medicinal products.

### ***Problem solution – Proposed legal intent***

- It is proposed to legally require the MAH to consult patients and healthcare professionals for developing materials used as aRMM to ensure that are legible, clear and easy to use and designed in such a way as to enable users to understand the measures and act appropriately (proposed to amend Article 104(3)(d) of Directive 2001/83/EC<sup>76</sup>).

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Module XVI, and there could also elaborate on the need to focus stakeholder consultations on the design of aRMM that are usable and enable acting appropriately in healthcare.

## **28. Action 'Requiring MAHs to implement joint aRMM'**

### ***Problem statement***

- Currently there is no legal provision obliging MAHs for medicinal products containing the same active substance that have the same additional risk minimisation measures (aRMM) to develop and disseminate identical aRMM materials.
- This results in unnecessary burden, both for the national competent authorities who have to review and approve the various aRMM materials submitted by multiple MAHs, and for

<sup>73</sup> Goedecke T, Morales D, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions: systematic review and methodological considerations. *Br J Clin Pharmacol.* 2018; 84: 419-433. doi: [10.1111/bcp.13469](https://doi.org/10.1111/bcp.13469);

Bahri P, Morales DR, A Inoubli, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel Analysing Stakeholder Safety Engagement Tool (ASSET). *Drug Saf.* 2021; 44: 193–209 (epub 30 Oct 2020). doi: [10.1007/s40264-020-01005-3](https://doi.org/10.1007/s40264-020-01005-3);

further ongoing research between EMA and an academic partner confirms current limitations in a RMM to be overcome, publication awaited.

<sup>74</sup> Released for public consultation in 2021 accessible at: [https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools\\_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf).

<sup>75</sup> [https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iv\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iv_en.pdf)

<sup>76</sup> Article 104(3)(d). of Directive 2001/83/EC: "As part of the pharmacovigilance system, the marketing authorisation holder shall:[...] (d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a."

healthcare professionals and patients who may get confused when seeing differently looking materials when e.g. switching between generic products and/or the originator product.

- It is also understood that industry representatives at the EMA Industry Stakeholder Platform on 17 November 2021 prefer aligned aRMM for generic products to “avoid confusion with patients and healthcare professionals with different label information and/or risk minimization for otherwise interchangeable generics”. As a particular example, concerns have recently been voiced by patient representatives towards EMA over obstacles and inconsistencies with implementing aRMM for generic products containing thalidomide, lenalidomide or pomalidomide across jurisdictions worldwide. They also considered that envisaged advantages of harmonised aRMM and their implementation by multiple MAHs jointly<sup>77</sup> may be beneficial for patients and their treating healthcare professionals in the EU.

### ***Problem solution – Proposed legal intent***

- It is proposed to add a legal provision demanding MAHs of products with the same active substance to implement aRMM jointly if the regulatory aRMM requirements for the concerned products are the same (proposed to amend Article 104(2) 1<sup>st</sup> sent. of Directive 2001/83/EC<sup>78</sup>).

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Modules V and XVI. This could include guidance to use, in educational aRMM materials, the name of the active substance in addition to the invented name of the product in the support of patients.

## **29. Action ‘Enhancing pharmacovigilance for identifying and preventing misuse and abuse’**

### ***Problem statement***

- The legal scope of pharmacovigilance includes adverse effects resulting from use of the medicinal products outside the terms of the marketing authorisation.<sup>79</sup> In GVP Module VI this is interpreted as to include misuse and abuse of products.
- While misuse and abuse of medicinal products is a cause for patient harm in Europe<sup>80</sup>, its monitoring currently do not benefit from any specific methodological framework in the EU. Spontaneous reporting of adverse reaction has shown to be an inadequate method for detecting and quantifying the misuse or abuse potential of medicines.

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<sup>77</sup> Mueller M, Lewis DJ. Implementation of a pregnancy prevention programme (PPP) with a controlled distribution system (CDS) for the generic teratogenic phthalimides thalidomide, lenalidomide and pomalidomide. *Ther Innov Reg Science*. 2021; 55: 1155-1164.

<sup>78</sup> Article 104(2) 1<sup>st</sup> sent. of Directive 2001/83/EC: “The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.”

<sup>79</sup> Article 101(1) sentence 2 of Directive 2001/83/EC: “The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients’ or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.”

<sup>80</sup> EMCDDA, European Drug Report, 2019. [https://www.emcdda.europa.eu/system/files/publications/11364/20191724\\_TDAT19001ENN\\_PDF.pdf](https://www.emcdda.europa.eu/system/files/publications/11364/20191724_TDAT19001ENN_PDF.pdf)

### ***Problem solution – Proposed legal intent***

- While no immediate proposal for a legal solution is made in this Concept Paper, the Steering Committee of the multi-institutional Opioid Crisis Prevention Initiative led by EMA offers to develop possible solutions based on EMCDDA's and Member States' experience<sup>81</sup> - also acknowledging the European Commission's previous concerns and the work of the Horizontal Working Party on Drugs of the Council of the EU (HDG) -, and asks the European Commission to consider a legal basis for enhancing safety monitoring and prevention of misuse and abuse of medicinal products.
- In this context, consideration could also be given to acknowledge the relevance of misuse and abuse potential in data requirements, assessment and decision-making for granting and maintaining marketing authorisations.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP, in particular in Modules V and VI and possibly Modules VII and XVI, and in pre-authorisation guidance.

## **30. Action 'Using digital tools and artificial intelligence for pharmacovigilance'**

### ***Problem statement***

- In its preamble, the current legislation demands the continuous update of pharmacovigilance taking into account scientific and technical progress.<sup>82</sup>
- The increasing availability and feasibility of applying digital tools, in particular those making use of artificial intelligence, to health and other relevant data collected through digital media and devices are expected to enhance pharmacovigilance processes, including risk minimisation in healthcare.
- While it is considered that the current legislation already provides for amending pharmacovigilance with technical progress, more legal underpinning might support the safe and effective use of digital tools for this purpose.

### ***Problem solution – Proposed legal intent***

- While no immediate proposal for a legal solution is made in this Concept Paper, it is proposed to explore with the European Commission the expected opportunities of digital tools and artificial intelligence for pharmacovigilance and which legal provisions might support data privacy and security and ensure that MAHs and the EU regulatory network can use new technology effectively.

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<sup>81</sup> Monzon E, Taam MA, Mesquidou MC, Bahri. Balabanov P, de Fays L, Herrera CA, Noor A7, A. Saint-Raymond, Straus S, Inoubli A. Preventing an opioid crisis in Europe: an overview of measures to support medicines regulators. *Drug Saf.* 2021; 44: 1399 (O-007).

<sup>82</sup> Preamble of Directive 2001/83/EC: "(54) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress."

## ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP as well as methodological guidance on e.g. EudraVigilance, signal detection and investigation and post-authorisation safety studies.

### **31. Action 'Providing for regulatory action in the case of serious and/or persistent MAH pharmacovigilance non-compliance'**

#### ***Problem statement***

- The current legislation provides for taking penalty action towards MAHs.<sup>83</sup> However, the penalty procedure<sup>84</sup> is lengthy and often disproportionate, and does not always obtain the desired results in terms of corrective action, at least not in timely manner for patient safety.
- There are no specific legal provisions regarding which sanctions and/or enforcement actions and, most importantly, action to protect patient and public health should be taken and who should take such action if an MAH does not take appropriate corrective and preventive measures and MAH pharmacovigilance non-compliance persists, or if an MAH does not comply with requested data submissions.
- This is considered a limitation in the legislation, in particular if critical inspection findings may jeopardise the safety of the medicinal products and/or if there is otherwise indication that competent authorities can possibly not fulfil their pharmacovigilance obligations with the confidence that all data have been gathered, processed and submitted by the MAH, or if there is indication that risk minimisation measures (RMM) might not have been disseminated by the MAH (incl. insufficient documentation of RMM dissemination).
- Reference is made to the US FDA policies on warning and notice of violation letters as relevant practical example of possible actions from another major jurisdiction.<sup>85</sup>

#### ***Problem solution – Proposed legal intent***

- It is proposed to have measures available for gradual and proportionate actions with the penalty procedure only as a last resort, underpinned by a legal framework for considering and taking regulatory action if a MAH is found to be seriously or persistently non-compliant, including in the absence of complete documentation.
- The following new types of action to resolve MAH non-compliance and ensure proper and immediate risk minimisation could be considered (proposed to amend to Article 111(8) of Directive 2001/83/EC):
  - Warning letter, non-compliance statement or infringement notice, possibly being published ('public shame');
  - Compulsory education and facilitation measures;

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<sup>83</sup> Article 111(8) par. 3 of Directive 2001/83/EC: "Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties."

<sup>84</sup> Commission Regulation (EC) No 658/2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004

<sup>85</sup> US FDA; <https://www.fda.gov/drugs/enforcement-activities-fda/warning-letters-and-notice-violation-letters-pharmaceutical-companies>

- Urgent variation of the marketing authorisation;
  - Suspension of the marketing authorisation if the case allows for this without negatively impacting patients;
  - Advertising ban;
  - Further inspections;
  - Amendments or suspension of clinical trials due to product-specific safety concerns or uncertainty about the safe and ethical conduct of the trials, also in the absence of complete documentation.
- Additional observation: If the European Commission is in favour of competent authorities to use the penalty procedure more often in the future as a dissuasive tool, a revision of the penalty regulation is considered warranted to make the procedure more proportionate, practical and feasible.

### ***Proposed solutions in guidance***

The new legal provisions would be further detailed in GVP Modules I and III, and the applicable guidance on penalties.