COMMENTS FROM CMDh

Accuracy consultation of CMDh on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

If necessary, please add additional rows.

Page, line	Comment
Chapter 3 and further	In some instances it is unclear whether reference is made to MRP/DCP or CP or both and the report seems to put more emphasis overall on CP. The contents should be clear and balanced.
Pages 6 and 18 – line: "EMA Committees: The Study Team participated in the meetings of 2 Committees: CHMP, and CMDh."	CMDh is incorrectly labelled as 'EMA Committee'.
Page 9, line 47	"…a majority of new, innovative medicines passing through the centralised authorisation procedure in order to be marketed in the EU." While formally correct, in reality all virtually innovative medicinal products are submitted in the centralised procedure.
Page 10, line 4	"…MRP and DCP allow country selection, where the choice for commercial and reimbursement decisions are generally considered." An additional important consideration that for the choice of the Reference Member State has been the (perceived) performance of the national agency.
Pages 10 and 98 – line: "The CP provides a solid and robust procedure, which is preferred by research-based companies; whereas MRP and DCP allow country selection, where the choice for commercial and reimbursement decisions are generally considered."	The text suggests that MRP/DCP would be less solid/robust compared to CP. CP and MRP/DCP are in theory only directly comparable in situations in which MA is requested in all member states simultaneously. Especially during COVID pandemic and general situations of medicine shortages MRP/DCP have proven to be of great added value in enabling targeted and fast availability of products in specific member states. Added value and flexibility of MRP/DCP compared to CP is also elaborated upon on page 102.
Pages 10 and 99 – line: "Increased visibility of DCP and MRP timeframes would be welcomed given the high level of heterogeneity across MS. […] Regarding the DCP and MRP, procedures are less burdensome for the system, though less transparent, predictable and efficient for applicants themselves due to inconsistencies and an unharmonised application of the regulation across	The text seems to be in contradiction with the fact that timetables for MRP/DCP have been determined and are publically available. Chapter 4 of the Directive provides the overall timetable, and detailed timetables are publicly available on the CMDh website – next to best practice guidelines to which RMS and CMS are bound. The only difference in timing for marketing authorisation can occur at the national level after the EU procedure has been finalised. If the text instead refers to the <u>adherence to</u> the applicable timetables for the validation, clock-stop and/or national phase of the MRP/DCP and not the <u>clarity of</u> applicable timelines in general, then this should be specified.

Member States. The current MRP process allows countries to have additional requirements and administrative controls, which leads to procedures being delayed in frequent cases" Page 157 – Finding 25 MRP/DCP timelines are not always respected: "Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources of formalising and redefining timelines …[…]… Industry stakeholders have more clarity on timelines"	
Pages 13 and 154 – "Potential action: Eliminate RMPs for generic products, creating the opportunity to refer to active substance profiles in the pharmacopeia."	Please add EC and CMDh as relevant stakeholders.
Pages 13 and 155 – "Potential action: Simplify the Variations legislation in line with the simplifications done for variations concerning veterinary medicines. This would notably include allowing MAH to make Type IA variations directly in the databases without passing via NCAs."	Please add EC and CMDh as relevant stakeholders.
Pages 13 and 157 – "Potential action: Increase the work towards harmonising definitions and categorisation of products across Member States. This could be facilitated through EMA adopting guidelines on European standards/best practices."	Could this be further elaborated upon? Additional guidelines may not solve the issue at hand.
Pages 13 and 157: "Potential action: Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources or formalizing and redefining timelines."	Please add more context to potential action – this is not primarily a timeline issue but related directly to the quality of the application dossier. Please also refer to HMA/EMA Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines.
Pages 24 – 28, section 2.2.1	CMDh is not mentioned as one of the key actors of the network. Please note that CMDh is not a committee of the EMA.
Page 28 - line: "Apart from national authorisations	MRP and DCP are procedures leading to NATIONAL marketing authorisations. The

in each Member State, three different procedures can be used by applicants looking to have a product authorised in Member States of the EEA"	'national authorisations' referred to in the indicated sentence are in fact 'purely national authorisations' where a product is only registered in a single EU/EEA country. Hence, there are three procedures leading to national authorisations and one leading to a central (EU-level) authorisation.
Page 28 – line: "These procedures vary based on whether or not the medicinal product has already been authorised in a Member State, on the scale to which the product will be authorised at EEA level, on the type of product as well as on the involved authorities providing the required scientific assessment for the quality, efficacy and safety of the product."	The type of procedure chosen/mandatory for a particular product does not depend on the authorities involved. In fact, the authorities involved depend on the chosen/required procedure and, in the case of a national marketing authorisation, the Member States in which the company wishes to market the product.
○ Page 29, Fig. 4 table row 'Market authorisation procedure overview', table columns on DCP – line: "The Market Authorisation is granted by NCAs and notified to the applicants and the EMA"; ○ Page 38 – line: "In accordance with Article 21, once the National Competent Authority has issued a market authorisation, it must take the necessary measures to notify the applicant as well as EMA"; ○ Page 38 – line: "The fact that mutual recognition has been granted is to be communicated to the applicant, the Reference Member State, EMA as well as all concerned Member States"; ○ Page 39 – line: "Furthermore, the applicant must communicate the application to EMA, specifying Member States where an application has been submitted, as well as the dates of submission and copies of market authorisations that already have been granted. The applicant should also draw EMA's attention if the medical product is under examination for authorisation	In accordance with Art. 22(2)c of Directive 2001/83/EC, 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. Such provision is not included for authorisations granted through an MRP or DCP were no post-authorisation conditions or obligations are imposed on the MAH in accordance with mentioned articles. The text therefore seems factually incorrect – or are these sentences referring to reporting to the article 57 database? Further, in regards the sentence "[t]he fact that mutual recognition has been granted is to be communicated to the applicant, the Reference Member State, EMA as well as all concerned Member States" (page 38): please note that the RMS is the one reporting, not the one that needs to be reported to.

in any Member State”;	
Page 29, Diagram MRP/DCP	The scientific assessment required will be. // Text unclear? In case a disagreement arises , referrals procedure with EMA can take place CMDh Referrals are not mentioned throughout the document (at least not explicitly). However, this procedure at the level of the CMDh is an effective measure to resolve disagreements of MS at the end of MRP and DCP and remove burden from the overall system (e.g. less Referrals at CHMP)
○ Page 29 – Fig. 4: table row ‘Market authorisation procedure overview’; ○ Page 38, section ‘Conditions under which the procedure is conducted’ – lines: “Articles 29 to 31 detail the procedure that has to be conducted should a disagreement arise between Member States in the context of a mutual recognition procedure” and “If the Member States do not reach an agreement, a number of referral procedures can be initiated, in accordance with articles 29 and following of the Directive (See sub section 2.5.3)”:	Referrals are not restricted to the MRP but are also started in case of a DCP were at the end of the procedure disagreement exists between RMS and one or more CMS in regards the B/R balance of the medicinal product. Referrals resulting from such disagreement in either the MRP or DCP are handled at CMDh level. (Only) if the referral cannot be resolved by CMDh, the case is referred to the CHMP. Further, an Art. 30 referral is a harmonisation referral where differences in labelling content have arisen between MS. These referrals follow from a list of products drawn up by the CMDh upon a proposal from the Member States.
○ Page 29 – Fig. 4: ‘Outcomes’; ○ Page 39, section ‘Market Authorisation subjected to specific Obligations (Article 22 of Annex I of the Directive)’ – line: “The authorisation has to be renewed after five years based on a consolidated renewal application” ○ Pages 42 – 43, section 2.5.2 ‘Renewals’	The text suggests that there is a difference with regard to the renewal of the marketing authorisation, validity of the marketing authorisation after renewal, the required contents of the renewal dossier and objective of renewal between products authorised via the MRP or DCP on the one hand or the CP on the other. This is not the case. Art. 24 of Directive 2001/83/EC and Art. 14 of Regulation (EC) No 726/2004 contain identical provisions, with the exception of references to the authorising authority (national competent authorities or Member States vs EMA or Commission) and legislative basis (Directive vs Regulation).
Page 30 – line: “Only products that have already been authorised in a Member State through a national procedure are eligible for mutual recognition”	Please note that MRP and DCP also lead to national authorisations. What is meant in this sentence is the purely national procedure. Further, this information is incomplete. Also products that have been authorised in several Member States via an MRP are eligible for another MRP. Via this “second wave” MRP the product is registered in additional Member States. This MRP is known as the

	'repeat-use procedure' (RUP).
Page 33 - line: "Whilst EMA has developed mechanisms in order to facilitate the submission of applications for the centralised procedure, Directive 2001/83/EC does not set such steps for the decentralised and mutual recognition procedures. Nonetheless, it should be pointed that, as stated under Articles 17 and 18 of the Directive, Member States can take measures allowing the avoidance of double-applications in various Member States."	Interpretation of Article 17/18 is not related to pre-submission meetings. Therefore, the added remark seems out of place. In addition, 'EMA' and 'Directive' are not same-level elements and can therefore not be compared. In this light it is further to be noted that Regulation (EC) No 726/2004 also does not provide for pre-submission mechanisms, as is mentioned in the paragraph above.
Page 34 – line: "The European Medicine Agency's Committee for Medicinal Products for Human Use (CMDh) drafts guidelines…"	'CMDh' should read 'CHMP'.
Page 37	Typo: below heading 2.4.2. Decentralised Procedure: Titre III instead of Title III
38 „Conditions under which the procedure is conducted"	Commission's guidelines defining a "potential serious risk to public health" are set out in Article 29 (2) of Directive 2001/83/EC), not in Article 28.
Page 38, section 2.4.3 'Mutual recognition procedure'	Information on the repeat-use procedure (RUP) is lacking.
40, 4-5	As the text makes reference to the pharmacovigilance mechanisms set by Regulation (EC) No 726/2004, those are provided by Articles 21 (not 22) to 29 and the regulation as amended states that the provisions laid down under Article 104 of Directive 2001/83/EC (not 106). Maybe the authors have not used the current version of Regulation (EC) No 726/2004 under the headline "Pharmacovigilance mechanisms under the responsibility of EMA"?
40, 4-5	As the text makes reference to the pharmacovigilance mechanisms set by Regulation (EC) No 726/2004, those are provided by Articles 21 (not 22) to 29 and the regulation as amended states that the provisions laid down under Article 104 of Directive 2001/83/EC (not 106). Maybe the authors have not used the current version of Regulation (EC) No 726/2004 under the headline "Pharmacovigilance mechanisms under the responsibility of EMA"?
42 „Pharmacovigilance mechanisms undertaken at national level"	The obligation of the MAH to record and report suspected adverse reaction is stated in Article 107 Directive 2001/83/EC not in its Article 104.
Page 45, on Type IA variations for centrally authorised products – line: "Within 30 days the	Type IA variations are only validated, not assessed. This applies to variations submitted for centrally and nationally (MRP/DCP) authorised products. Please refer to Chapter II

Agency will take measures allowing to assess the notification (see below)".	and III of the Variation Regulation.
46, 10	As reference is made to Article 34 of Regulation (EC) No 726/2004, this Article is dealing with veterinary medicinal products.
46 „Variations under the decentralised and mutual recognition procedures"	Regulation (EC) No. 1234/2008 is wrongly described with Regulation 1234/2008/EC (in the format of Directives).
Page 46, Minor variations	"After consulting other concerned authorities, the national competent authorities in the Reference Member State acknowledges that the notification received is valid." – "valid" should be replaced by "approvable".
Page 46, Major variations	"Once the applicant has submitted a request, the NCA of the Reference Member State acknowledge the valid application has been received. Within 60 days, the NCA must prepare an assessment report and a decision project, which will be forwarded to other competent authorities. Under certain circumstances the procedural timeframe may be reduced or extended up to 90 days. Within 12 days following the receipt of the report and the decision, the relevant authorities of concerned Member States will recognise the decision. Should a disagreement arise based on a potential risk to human health, procedures laid under Article 29 shall apply (Please refer to Referrals)." The RMS prepares no "decision project" but just the assessment report. Within 30 days following the receipt, CMS will recognize, not 12 days.
Page 46 on Type II variations for centrally authorised products – line: "Once the applicant of the variation has submitted a valid application, EMA must issue an opinion within 60 days. The time frame can be extended up to 90 days in certain cases."	As is the case for nationally authorised products, and in accordance with Art. 16.2 of the Variation Regulation, EMA may also reduce the timeframe of a Type II variation having regarded to the urgency of the matter.
Page 46, on type IB variations for nationally authorised products – line: "After consulting other concerned authorities, the national competent authorities in the Reference Member State acknowledges that the notification received is valid."	The description of a Type IB variation is incomplete. After validation, the procedure is started and within 30 days the RMS has to issue an opinion. In case of an unfavourable opinion, the applicant has 30 days to respond. Upon receipt of the response, the RMS has to issue an opinion within 30 days. In case of rejection, the CMS and applicant are informed of the grounds for rejection. In case of a favourable opinion, all relevant Member States have to vary the marketing authorisation within the timelines given in Art. 23 of the Variation Regulation.
Page 46 – 47, section 'Extension of marketing authorisations (Article 19)';	First, extensions of marketing authorisations are not handled through variation procedures but shall be evaluated in accordance with the same procedure as for the

	initial authorisation (210 days), but this is unclear from the text as the section is merely listed under section 2.5.4 'Variations' without adequate/sufficient explanation. Second, extensions of marketing authorisations can equally be submitted for centrally authorised products (in the report, the information is only included under subsection 'Variations under the decentralised and mutual recognition procedure').
Page 47, extension applications	Last paragraph on EMA guidance should be deleted as this is a chapter on MRP/DCP.
Page 47, subsections 'Work sharing procedure (Article 20)' and 'Grouping variations'	Worksharing and grouping of variations can equally be submitted for centrally authorised products (in the report, the information is only included under subsection 'Variations under the decentralised and mutual recognition procedure').
Page 47, subsection 'Work sharing procedure (Article 20)'	Worksharing can be applied if the underlying products belong to the same MAH.
Page 47, worksharing	"It allows an applicant to submit a group of Type B or a group of Type II variations, or a group of variations affecting various marketing authorisations." To be corrected to: "It allows the same MAH to submit a single variation or a group of variations affecting more than one marketing authorisation in more than one member state."
Page 47, subsection 'Grouping variations' – line "The grouping variation procedure is set under Article 7.2 of the Variation Regulation. It allows Market authorisation holders to submit multiple IA variations affecting either one or several medicinal products."	The text incorrectly suggests that grouping can only be applied to Type IA variations. Instead, grouping of variations is also permitted in cases specified in Articles 7.2 and 13d.2 and in Annex III of the Variation Regulation.
Page 47, grouping	"The grouping variation procedure is set under Article 7.2 of the Variation Regulation. It allows Market authorisation holders to submit multiple IA variations affecting either one or several medicinal products. Grouped variations must be distinguished from the workshare procedure. Although grouped variations can be subjected to the Work sharing procedure, as long as all medicinal products are affected by the same type of variations." To be corrected to: "The grouping variation procedure is set under Article 7 of the Variation Regulation. It allows marketing authorisation holders to submit multiple IA variations affecting either one or several marketing authorisations or several variations of different types affecting one marketing authorization in one single application. Grouped variations must be distinguished from the worksharing procedure. Although grouped variations can be subject to the Worksharing procedures, as long as all medicinal

	products are affected by the same type of variations.
47 (2.5.5 Sunset clause monitoring)	With reference to the provisions which contain the sunset clause it is the other way round: In Directive 2001/83/EC it is Article 24 and in the Regulation (EC) No 726/2004 it is Article 14
Page 47, SSc	"It should be stressed that the marketing authorisation remains valid if at least one presentation of the existing product is placed in at least one Member State". This is not correct for MRP/DCP. CMDh published guidance: "The individual MS will therefore need to take account of the specific situation for its own market. It should be noted that the application of the sunset clause is a national decision to be made by each concerned member state."
Page 68, line 17	"…as there is an equal distribution of CMS across Member States, there exists the potential to further distribute RMS". The Applicants choose the Reference Member State; a "distribution" by regulators in order to equal the distribution across Member States is not possible.
Page 85 - line: "Room for improvement was identified in relation to pre-submission activities for the DCP and MRP"	The underlying source for this conclusion is not clear, but seems to be based on the survey responses as displayed in figure 34 on page 86. The questionnaire, however, does not seem to focus on pre-submission meetings for industry but rather on the dialogue between RMS and indicated CMS's prior to filing the application. In most cases such dialogue is not warranted as no pre-assessment takes place in MRP/DCP. The first question (guaranteed identical application files) is not up to Member States in any case. The onus lies with the company to make sure an identical application has been filed.
Page 85 - line: "Managing advice from various NCAs can be difficult for companies. For instance, where the requests are submitted in parallel and the outcome is not completely superimposable, complications can exist with a difficult implementation of different recommended approaches."	It is up to the company to request parallel scientific advice in several member states. The alternative route for companies is to request sole advice to the RMS.
Page 92, line 16	The number of compassionate use programmes performed e.g. in Germany is approx. 12-14 per year.
Page 99, line 4-5	Timeframes for MRP and DCP are published as flow charts on CMDh website. The timeframes are binding.

Page 99, lines 19-23	„Regarding the DCP and MRP, procedures are less burdensome for the system, though less transparent, predictable and efficient for applicants themselves due to inconsistencies and an unharmonised application of the regulation across MS. The current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases. “ This view is surely not shared. MRP and DCP are very transparent procedures, informing the applicants about all steps during the procedure. The outcome is predictable if existing guidelines are considered in the application. The complete procedures are processed in an absolutely harmonized way, with the exception of some very few administrative national requirements that are well-known and published on the CMDh website. CMDh and HMA are continuously working on reducing these requirements which are all only concerning submission details but not the content of the dossier. Procedures are only delayed in cases where the published information is not regarded in the submitted documents. Only the national phase after finalization of the EU procedure is handled on a national basis.
Page 100, last paragraph	The numbers for MRP/DCP seem to be fluctuating in the same way as for CP. In figure 50 nearly the same curve is headed with “remained consistently high”.
Page 111, paragraph on timelines	Single person’s views should not be used in the final report. The overall timelines in MRP/DCP are well respected by the member states. It should be made clear that only the national phase might be handled differently by the member states. Innovations are furthermore not submitted via MRP/DCP but the CP is used.
Page 116 – line: “In addition, benefit risk assessment decisions are made available to the public, as European Public Assessment Reports (EPARs) are available following the product authorisation. The assessments are of high quality, as confirmed by industry stakeholders and the product case studies and are adhered to by CHMP and PRAC.”	In accordance with Art. 21 and 106 of Directive 2001/83/EC, public assessment reports are also made available for MRP/DCP.
Page 118, line 24-26	Same comment as above on page 99, lines 19-23, this summary and interpretation of MRP/DCP is not shared.
Page 118, line 27-30	The national requirements are published and well-known and reduced continuously with efforts of CMDh and HMA. Single examples should not be mentioned in this report and especially the case on individual equivalence studies is legally not correct and this is already reflected in published CMDh documents.

Page 118, line 31-42	It was always important for NCAs to keep the national responsibility for the legal status. Which status is possible in which MS is publicly available information, so should be no surprise for applicants.
Page 118 - line: "Administrative burden was identified by industry in relation to the DCP and MRP, particularly due to the diverging views that could be provided by Member States. For MRP/DCP, burdens can arise due to unharmonised interpretation and application of legislation. This makes procedures less transparent, predictable and efficient for applicants themselves due to inconsistencies across MS.	Diverging views on interpretation of legislation can occur both in CP as well as MRP/DCP. Cases at hand can be discussed in CMDh/CHMP. Furthermore, the reduction in numbers of CMDh referrals (see page 124) shows that in virtually all cases consensus is reached.
Page 118- line: "For example, the current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases. Another example is the case where a CMS may demand that the applicant demonstrates equivalence with other products on its own market, despite a European reference product existing."	This takes place outside the context of European procedure (for instance during reimbursement trajectory, related to substitution). If CMS files a request of this nature during MRP/DCP, it is denied as evidence of bioequivalence with the chosen reference product is sufficient. Text should there be read in correct context.
Page 126, lines 1-2	It is not possible in MRP/DCP variations to "complete own assessment and procedure". The variation is a joint procedure with a common outcome, there is no room for "own assessment". Furthermore, the CMDh is especially promoting the use of the worksharing procedure in order to reduce national parallel assessments. As this is a voluntary procedure for the applicant but not the NCAs CMDh is using any opportunity to convince applicants of the advantages of the worksharing and encourage its use.
Page 126, line 6	It should not read "to update the variations" but "to update the variations guideline".
Page 126, paragraph on timelines	Usually the adaptation to the outcome of a safety referral is a type IA variation which is automatically started after receipt in the RMS or a type IB variation. A start date delay of 118 is surely an exceptional case. Most of the procedures are started according to the timeframes established. Most start delays occur due to invalidation issues because of incomplete variation application submissions. After finalization of the procedure the possible implementation date for applicants is written in the law, applicants do not need to wait for national approval longer than the timeframe stated in the regulation. They can

	immediately implement the changes.
Page 134, last paragraph	The new veterinary legislation is not yet implemented. Its success should be explored before it is recommended for other procedures. Furthermore, it is not correct that the data for variations not requiring assessment does not have to be submitted in addition to the common database. The current view of CMDv is that a submission of the eCTD sequences to NCAs is still necessary in order to keep the eCTD history correct.
Page 137, figure 82	CESP as a tool is used for post-authorization as well. (Same as eAF and eSubmission Gateway)
Page 152, line 2	"Pre-submission procedures allow for refining applications and screening those that have little chance of authorisation at an early stage…" Screening is meaningless as validation of submissions is strictly formal and does not consider the scientific content; there is simply no mechanism that would allow the rejection of obviously premature submissions. There have been submissions apparently timed in a way that crucial data from the pivotal study would become available just in time for the response to the list of questions (or the list of outstanding issues).
Page 154, 155, finding 15 and 16	Add European Commission and CMDh to the relevant stakeholders (same applies for page 13)
Page 157, finding 23	The national requirements by single member states concern submission documents and are well-known. CMDh and HMA and the concerned NCAs are continuously doing all efforts to reduce these requirements.
Page 157, finding 25	The delay of procedure starts and restarts is not only a timeline question and not only related to MRP and DCP but is closely related to the quality of the submitted dossiers for both, CAPs and NAPs. Incomplete submissions lead to invalidations and further requests. This topic has already been discussed and guidance is published as "HMA/EMA BPG on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines.
Pages 164 - 165, Fig. 97 'Decentralised procedure'	'National Competent Authority' should read 'Reference Member State', as was done for the MRP (Fig. 98). The flow-chart is in details incorrect. It reads as if break-out sessions occur during every DCP whereas in reality these sessions are very rare. The flow-chart reads as if in all cases of no consensus a CMDh referral is started. However, a CMDh referral is only started when the RMS considers the benefit/risk (B/R) balance of the product to be positive whereas one or more CMS deem the product not approvable on the basis of a potential serious risk to public health (PSRPH). If the RMS concludes that the B/R of the product is

	negative, the product is deemed not approvable regardless of the opinion of the CMS on the B/R, since only a positive assessment by the RMS can be the reason for a CMS to raise a PSRPH concern. The flow-chart also implies that the national phase of the DCP normally happens after Day 275, whereas this is only the case if a CMDh and CHMP referral are required to reach consensus. Normally, the national phase starts directly after Day 210 of the procedure. General note: Fig. 97 should be corrected in line with the DCP flow-chart provided by the CMDh (June 2020, CMDh/080/2005, Rev. 4) and the CMDh Best Practise Guide for Decentralised and Mutual Recognition Procedures (February 2020, CMDh/068/1996, Rev.12).
Page 166, Fig. 98 'Mutual Recognition Procedure'	The flowchart is in details incorrect. The MRP only has one round of assessment, not two. The procedure ends at Day 90 and is either directly followed by a national phase or referral + subsequent national phase. Any break out session usually occurs at Day 75, so within the procedure timeframe and not, as suggested by the flow-chart, after the end of the procedure. If no consensus has been reached by Day 90, the procedure is referred to the CMDh, which is not presented correctly by the flow chart. Only if the issue is not resolved at CMDh level the matter will be further referred to the CHMP. As already indicated above, the national phase of the MRP usually starts directly after Day 90. Only in case of a referral is the national phase delayed. This is not correctly reflected in the flow-chart. General note: Fig. 97 should be corrected in line with the MRP flow-chart provided by the CMDh (February 2020, CMDh/081/2007, Rev. 3) and the CMDh Best Practise Guide for Decentralised and Mutual Recognition Procedures (February 2020, CMDh/068/1996, Rev.12).

Accuracy consultation of Pharmaceutical Committee on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

Comments from the European Medicines Agency (EMA)

Ref: EMA/370230/2020

Executive Summary (p 5-13)

Page, line	Comment
General EMA comment on the EY report	EMA noted several inaccuracies or incomplete descriptions of EMA processes in the report. The below list of EMA comments is not exhaustive and focusses on correcting some important factual mistakes or misunderstandings. Readers are advised to refer to EMA's website and to the following publications in particular: EMA User Guide for micro, small and medium-sized enterprises From laboratory to patient: the journey of a medicine assessed by EMA EMA Pre-Authorisation guidance EMA Post-Authorisation guidance
Page 7	The report states that the increased complexity is notably through the creation of PRAC, new working parties as well as the PRIME scheme. However, PRIME itself has not led to complexity or increased meeting days but is in fact a system to provide agility and focus in dealing with increasingly complex scientific and inter-committee discussions. Therefore it is in EMA's view not correct to include PRIME here in this paragraph.
Page 8	The statement that "some coordination on early advice is lacking" is unclear.
Page 8	The Agency's resource investment into PRIME is well balanced; therefore its mentioning in the context of the increase of staffing in relation to self-imposed activities appears disproportionate and should be deleted.
Page 8	The EY report refers to a "increased level of activity (+10% or above on the majority of tasks)" and also refers to a "+12% increase in staff between 2010 and 2017 (including contract agents and seconded national experts)". The manner in which these statistics are presented does not accurately reflect the underlying evolution of staffing and workload, which is of major concern to the Agency and has been formally highlighted in documents such as the 2018 and 2019 Annual Activity Reports (AAR). As highlighted in the AAR, the Agency has had to cope with a 10% imposed reduction in establishment plan posts between 2014 and 2018, while during the same period the application-related workload increased by 31%.

	Furthermore, significant new tasks such as the implementation of the Veterinary Regulation, GDPR, Medical Device regulation, Clinical trial regulation, were also assigned to the Agency during this period without any increase in the establishment plan staff The 12% increase in staff referred to in the report has come from a forced reliance on recruiting headcount on short-term contracts to cope with the growing workload, which is not a sustainable solution for the Agency in the longer-term.
Page 9	"Orphan designations by COMP should be better aligned with CHMP opinions": it should be noted that orphan designations are given early in development whereas CHMP opinions reflect the outcome of evaluation activities. Therefore, an 'alignment' as proposed by EY should/cannot be an objective as such.
Page 10	"As the CP involves duplicate procedures and formal involvement from NCAs, it requires a lot of capacity": The reference to 'duplicate procedures' here is incorrect; EY probably means to refer to the dual assessment process (ie the involvement of 2 Rapporteurs and their assessment teams).
Page 10	High workload by the CHMP is discussed with the suggestion to focus on what is critical and complex. However, the EY report does not refer to the need to avoid premature applications submitted by companies, which effectively lead to a waste of sparse CHMP resources.
Page 11	Whilst the EY report clearly acknowledges EMA's increased communication efforts, in particular via the EMA website and via other public communications, a third aspect of EMA's communication role should in our view also be reflected in the report as follows: • "EMA also plays a key role for the dissemination of important public-health communications within the EU regulatory network linked to EMA activities, by means of the Early Notification System and circulation of 'Lines to take' in order to help the EC and national medicines regulatory authorities to respond to external queries and to ensure that consistent and clear messages are provided to patients and health-care professionals across the EU in a timely manner."
Page 12	The action regarding the need to move beyond ad hoc flexibililty and develop clear strategies on how to address future challenges, is unclear as it stands and need to be read in the context provided in section 5.1.4.
Page 12	The action at the bottom of the page should make clear which processes it is referring to i.e. early advice processes
Page 12	Action 3 highlights the need to allow CHMP focusing on more critical and complex applications. However, the need to focus scientific discussions on what is complex and critical is applicable to all of EMA's scientific committees. It is therefore recommended to reword this action by replacing "CHMP" with "scientific committees".
Page 13	Action 17 calls for the creation of a mechanism similar to PRIME for SMEs. SMEs, however, already have access to PRIME as it currently stands.

Legislative background and context (p 21-49)

Page, line	Comment
Page 23	Figure 2 - column 'INPUTS': For completeness, the PDCO should also be listed.
Page 25, line 2-3	"Each committee establishes a number of working parties at the beginning of **each year** mandate". The stated yearly frequency is incorrect and should be revised as follows: "Each committee establishes a number of working parties at the beginning of **its** mandate" Replace reference to "The working groups" with "The working parties"
Page 29	The box setting-out the optional scope of the centralised procedure, has omitted the second indent of Art 3.2 of Regulation 726/2004. Medicinal products which either: (to be added:) "provide a significant therapeutic, scientific or technical innovation"
Page 29	The same legal principles apply for the 5-year validity and renewal of a MA granted via MRP or DCP or CP procedures. Therefore, the 3 boxes referring to "Outcome – Duration" should contain the same text for all 3 procedures in line with Art 14 of Regulation 726/2004 and Art 24 of Directive 2001/83. In addition, it should be noted that in the CP, a 'conditional MA' may be granted for which the validity ("duration") is only 1 year (renewable).
Page 33	2.3.2 "Other pre-submission activities of EMA": The heading is not reflecting what is described underneath ie the entire development support offered by EMA, and not just the 'pre-submission' step before MAA. "EMA development support activities in the pre-submission phase" would be a more appropriate title.
Page 33	Scientific advice: it is mentioned that "EMA established the Scientific Assistance Working Party (SAWP) within the CHMP" – this should be corrected to refer to the "Scientific Advice Working Party (SAWP)". In addition, this WP was not set up at the discretion of EMA, but was set up as required by Art 56.3 which requires a SWAP to be set up for both CHMP and CVMP '*with the sole remit of providing scientific advice to undertakings'*.
Page 33	The text talks about a "scientific advice team" to be appointed and the possibility for a meeting to be requested by the applicant. What is exactly meant is unclear. A more accurate description would be: "In order to provide the scientific advice, the scientific advice working party appoints two coordinators. A discussion meeting with the applicant might be held if this is necessary to provide the advice."
Page 34	Scientific guidelines: it is mentioned that the CMDh drafts guidelines, whereas this should be corrected to refer to the correct acronym "CHMP".
Page 34	Box 2: for ITF reference is made to '**Intervention** Task Force' instead it should read '**Innovation** Task Force'.

	The word 'sent' is missing in the sentence: 'If not, the scientific recommendation is to the European Commission within 10 days in order to collect comments.'
Page 34	With regard to the regulatory support for the development of medicines in relation to paediatric medicines the report makes reference to funding for paediatric studies. However, this is not the activity performed by EMA as this funding is provided through the European Union Framework Programmes for the development of medicines, with a view to the submission of an application for a paediatric-use marketing authorisation (PUMA). Instead the Agency's main activity to provide development support in this space is through the agreement of paediatric investigation plans including deferrals or waivers. More information can be found here: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans. This is then also the basis for the provision of incentives and rewards. The text should be corrected to exclusively focus on what is relevant for this review of EMA's activities.
Page 35	Regulatory support for medicines developments – orphan designation, last sentence: It should be noted that market exclusivity is triggered by the granting of the marketing authorisation, not by the placing on the market.
Page 35	The Quality By Design paragraph does not fit under the heading of 'Other specific support offered by EMA for the development of medicines'; the description of what Quality by Design is, as stated in the document, is also not correct. Instead, reference could have been made here to the Innovation Task Force of EMA, which was specifically set-up to offer developers of innovative treatments a platform for discussion of scientific, legal and regulatory aspects of their medicine with EMA at the early stages of development.
Page 36	List of documents to be transmitted to the European Commission as part of the opinion: "a proposed draft package" should read "a proposed draft package **leaflet**".
Page 37 Page 48	It is not clear why only a box for "MA exceptional circumstances" is included, and not a similar box for "conditional MA" as per Art 14-a of Regulation 726/2004 which is unique to the centralised procedure? Similarly, only the procedure for 'annual re-assessment' is mentioned in section 2.5.6 and not the annual renewal linked to the continuous monitoring of conditional marketing authorisations.
Page 40	2.5.1 Pharmacovigilance It is said that 'The holder of the marketing authorisation is also bound by the Regulation to respect a number of obligations regarding pharmacovigilance.' It should be noted that the pharmacovigilance obligations that are common to the centralised, decentralised/mutual recognition and nationally authorised products are laid down in Directive 2001/83.
Page 42	It is stated that 'EMA also plays a key part in pharmacovigilance mechanisms, as it is responsible, in collaboration with the European Commission and the Member States, to set a network which will allow data to be processed.' This is a rather

	unclear sentence but we understand that it probably refers to EMA's Eudravigilance system. In addition, it should be noted that assessment of PSURs and signal evaluation including for DCP/MRP and nationally authorised products take place at EU level by the EMA's Pharmacovigilance committee (PRAC).
Page 44	Table 8 Article 29 of Regulation (EC) No 1901/2006 is not triggered by the RMS but by the MAH.
Page 47	The paragraphs referring to Extension of MAs, Worksharing procedures and Grouping of variations not only apply to variations in MRP and DCP, but also apply to the Centralised Procedure.

WP 1: The European Medicines Regulatory Network (p 50 – 73)

Page, line	**Comment**
Page 50, 51	See also comment on page 8: The EY report refers to a "increased level of activity (+10% or above on the majority of tasks)" and also refers to a "+12% increase in staff between 2010 and 2017 (including contract agents and seconded national experts)". The manner in which these statistics are presented does not accurately reflect the underlying evolution of staffing and workload, which is of major concern to the Agency and has been formally highlighted in documents such as the 2018 and 2019 Annual Activity Reports (AAR). As highlighted in the AAR, the Agency has had to cope with a 10% imposed reduction in establishment plan posts between 2014 and 2018, while during the same period the application-related workload increased by 31%. Furthermore, significant new tasks such as the implementation of the Veterinary Regulation, GDPR, Medical Device regulation, Clinical trial regulation, were also assigned to the Agency during this period without any increase in the establishment plan staff The 12% increase in staff referred to in the report has come from a forced reliance on recruiting headcount on short-term contracts to cope with the growing workload, which is not a sustainable solution for the Agency in the longer-term.
Page 50	See also comment on page 7: The report states that the increased complexity is notably through the creation of PRAC, new working parties as well as the PRIME scheme. However, PRIME itself has not led to complexity or increased meeting days but is in fact a system to provide agility and focus in dealing with increasingly complex scientific and inter-committee discussions. Therefore it is not correct to include PRIME here in this paragraph.
Page 50	See also comment on page 8: The statement that "some coordination on early advice is lacking" is unclear.
Page 51	See also comment on page 8: The Agency's resource investment into PRIME is well balanced; therefore its mentioning in the context of the increase of staffing in relation to self-imposed activities appears disproportionate and should be deleted.

Page 52, figure 5 + Pages 167-169	Figure 5 as well as certain statements about EMA's working parties on pages 52 and 53 are not accurate – please refer to EMA's website for the correct information about the architecture of EMA's committees and Working Parties. See: https://www.ema.europa.eu/en/committees/working-parties-other-groups
Page 53, line 2	The CHMP's Biologicals Working Party (BWP) meets also 11 time/year, not only the SAWP
Page 53, line 10 + page 168	The Formulation Working Group and the Non-clinical Working Group, both linked to the PDCO, are not "temporary" working groups.
Page 59	Product case study 1: Tresiba It is stated that the pre-submission phase lasted approximately three years. It is not clear for EMA on which information this statement is based and what activities EY considered to fall under this phase. For instance, in the EPAR it is stated that the company applied for Scientific Advice in 2007, 2008 and 2009 – which is more than 3 years before MAA. The EY report also states that the assessment lasted 169 days whereas according to EMA's published Annex to the 2012 Annual Report, the assessment took 201 days (with an additional 164 days taken by the company to respond to questions). It is therefore not clear for the Agency on which information EY's statements are based. This applies also to other case studies included in the EY report.
Page 72, text above figure 24	EY's interpretation of EMA's staff increase does not reflect the underlying operational reality, because EMA staff working on initial evaluation activities also work on post-authorisation activities, and therefore staff movements over time need to be looked at together across both sets of activities. There was a decrease of -16 Full Time Equivalents (FTEs) in staff numbers working on post-authorisation activities between 2014 and 2015 (see Figure 24, page 72), at the same time that staff numbers working on initial evaluation activities increased by +15 FTEs. However, the number of staff working on initial evaluation activities from 2015 onwards remained relatively constant and aligned with the relatively constant level of initial applications received.

WP 2: Procedures preceding submission of Marketing Authorisation Applications (p 74 – 97)

Page, line	**Comment**
Page 74	In line with the EY distinction between 'pre-authorisation' and 'pre-submission' activities set-out in footnote 49, the reference to 'pre-submission activities' in the blue Synthesis part should be changed to 'pre-authorisation activities' as they refer to specific activities undertaken (and related statistics) at the level of EMA (as per EY's own definition)
Page 78	Product case 2: Fampyra

	It is stated that the Applicant provided additional data during the re-examination procedure; this is incorrect. According to Article 62(1) of Regulation (EC) No 726/2004: "The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion.", hence the applicant cannot provide new data. Applicants can only provide further clarifications and potentially also new analysis based on data submitted already during the initial MAA.
Page 78	For the composition of the SAWP it might be relevant to also mention the number of alternates as this is essential for the delivery of the working party.
Page 80	Regarding certification procedure for ATMPs, it is mentioned that 'The scope for the procedure concerns studies relying on quality data only or on quality and clinical data.' This should be corrected to refer to 'quality or **non**-clinical' data (as per article 18 of Regulation (EC) N0 1394/2007).
Page 83	Product case 4: Rapibloc The following sentence does not make sense: 'The PDCO submitted and opinion in September of 2014, and the PIP was agreed on in 2014.' EMA correction: The PIP was submitted end of 2013 (note: a PIP is submitted by the applicant but not by the PDCO), and the procedure started in January 2014. The opinion on the PIP application was adopted by the PDCO in September 2014. Regarding the following statement 'The case study presents an example where PIPs can pose a burden, with frequent revisions being necessary ': it should be clarified that, based on EU Legislation, a PIP is to be agreed very early during the product development. As product development progresses, new data/findings can indeed lead to the need to adapt the PIP. However, the PIP is agreed early in order to enable planning for paediatric data generation as early as possible during the product development.
Page 83	The statement that the majority of scientific advice requestor's at EMA were SMEs and that they account for 705 of all requests is not correct. Whilst SMEs make increasingly use of scientific advice over the years, they make up roughly around 30% of all requests. Figure 32 has in the legend the colours for a SMEs and medium/large pharmaceutical companies mixed up. Please also refer to the annual report 2019 (p 56): https://www.ema.europa.eu/en/documents/annual-report/2019-annual-report-european-medicines-agency_en.pdf
Page 85 + 95	The report notes that advice is provided at early stages on the national and the central level and calls for more coordination. However, what appears missing in the discussion is the reflection of the opportunities through complementary set-ups provided they are interconnected. On EMA side the early advice is provided through the Innovation task force (ITF); the equivalent on national level, where these exist, are the innovation offices from NCAs. Both areas are brought together in the EU Innovation Network (EU-IN), which is co-chaired by EMA and HMA (cf pp 88-89). The EU-IN is the place to progress such

	coordination. It appears therefore incorrect to refer to a "territorial conflict" between EMA and NCAs; instead the text should reflect the work from the EU-IN to correctly inform readers.
Page 88	The sentence "the procedure presented a welcome opportunity to reflect on how MAPs could be developed in the future" is very unclear and does not seem to fit within the paragraph explaining the PRIME scheme.
Page 90	The PRIME scheme has been implemented within the existing legal framework, the statement that it goes beyond the legislation is incorrect.
Page 96	Under 4.4.3 the contribution of pre-submission activities to the overall efficiency of the system is not 'purely theoretical' - it has been demonstrated

WP 3: Initial Marketing Authorisation Procedure (p 98 – 119)

Page, line	**Comment**
Page 98	Footnote 76 refers to an outline of each of the steps of the three procedures in the Annex (the page number is incorrect). The steps for the centralised procedure are however incomplete and partially inaccurate, e.g. notification of submission date of the application should precede the pre-submission meeting rather than follow it; the crucial step of the Day 120 List of Questions as adopted by CHMP is missing (amongst others). For an accurate description of the CP procedural steps, please refer to the following EMA webpage: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance#5.1-procedure-section
Page 105	The report concludes that the MRP/DCP is more suitable for generics. One of the reasons for the applicants' preference of MRP/DCP over CP for generics is claimed to be that if a 'company goes via the CP, it is likely to have to adopt the opinion of the most conservative Member State, as the CP is consensus driven'. This statement appears inaccurate. While scientific opinions by CHMP shall indeed ideally be taken by consensus whenever possible, the opinion can also be adopted if supported by an absolute majority of the members of the CHMP (see CHMP Rules of Procedure).
Page 107	Product Case Study 5: LAMZEDE The EY conclusion that the assessment time went beyond the legal deadline of 210 days is incorrect. The exact assessment time can be found in the Annex to EMA's annual report 2018 as published on EMA's website. The assessment took 203 days, with the company requiring 281 days to respond to questions.

Page 108	The report juxtaposes accelerated assessment (AA) and conditional marketing authorisation (CMA) stating that AA 'delivers a final verdict at the end' whereas CMA 'provides a temporary marketing authorisation for one year, which needs to be re-assessed and potentially renewed after this period'. It should be noted, however, that "Accelerated assessment" (only) concerns the timeframe in which an assessment is being conducted, and not the type of MA that is granted following such an accelerated assessment. Following CHMP assessment, whether accelerated or not, CHMP can recommend to grant either a 'standard' marketing authorisation or a 'conditional marketing authorisation' or a 'marketing authorisation under exceptional circumstances' as per the options in the EU legal framework, as appropriate. Therefore, the EY comparison of AA leading to a 'final verdict' as opposed to a 'temporary MA' granted by means of a conditional MA is oversimplified and flawed. Moreover, a "conditional marketing authorisation procedure' (as entitled on page 109) does not exist – conditional MA is a type of MA, not a type of procedure. The EY report also states that accelerated assessment procedures were reverted to normal timelines due to lack of evidence or capacity. The latter suggests that the European network was not able to accommodate procedures on an accelerated timetable due to insufficient availability of resources. However, this EY claim is not substantiated and is even incorrect as EMA never had to revert to a normal timeline based on lack of capacity in the network. The overall conclusion that the system puts the focus on patient safety is however correct.
Page 109	Product Case Study 6: KANUMA – EY states that the assessment time for this procedure was 154 days. The exact assessment time can be found in the Annex to EMA's annual report 2015 as published on EMA's website. The assessment took 152 days, with the company requiring 32 days to respond to questions.
Page 110	Product Case Study 7: ENTRESTO – The report claims that the assessment time for this procedure was 128 days. The exact assessment time can be found in the Annex to EMA's annual report 2015 as published on EMA's website. The assessment took 180 days, with the company requiring 66 days to respond to questions.

WP 4: Post-Marketing Authorisation Procedures (p 120 – 135)

Page, line	**Comment**
Page 134 + Page 154	EY states that a "reference to the Pharmacopoeia, which lists all relevant safety information, would simplify the process"; we understand that this should rather refer to the safety profile and the Risk Management Plan of the reference medicinal product (originator).
Page 120+ Page 125-7	The EMA notes the findings of the E&Y report identifying variations and RMPs as areas where the administrative burden can be reduced. To ensure its ability to handle the increasing volumes in post authorisation procedures, the Agency

	continuously tries to simplify, rationalise and remove duplications when handling post-authorisation changes within the current regulatory framework. In addition to the opportunities identified in the EY report, the legal framework covering the post-authorisation phase could benefit from being further rationalised in many other areas including but not limited to, the involvement of multiple committees on specific outcomes; opportunities for single assessment of ASMFs; review of the decision making process. Opportunities offered by technology advances could also be further exploited to allow online collaboration and sharing of information. Please also refer to the work of the "HMA Regulatory Optimisation Group" - see https://www.hma.eu/510.html
Page 120 + Page 123	"The complexity of Referrals is outweighed by the fact that they have been diminishing over the past years due to closer coordination efforts": Referral procedures are initiated to address concerns over the safety or benefit-risk balance of a medicine. The PhVig legislation, which came into effect in 2012, has introduced a stronger legal framework for proactively monitoring the safety of authorised medicines; this has significantly contributed to rationalising and reducing the use of this very complex regulatory tool (Referrals); not just due to "coordination efforts". For more information on Referrals see https://www.ema.europa.eu/en/documents/annual-report/2019-annual-report-european-medicines-agency_en.pdf
Page 123	Sunset clause - "This is to ensure marketing authorisations remain relevant": This is a very unclear statement. The 'Sunset clause' is a legal provision stating that the marketing authorisation of a medicine will cease to be valid if the medicine is not placed on the market within three years of the authorisation. The aim is to increase actual marketing of medicinal products and to avoid the administrative burden of maintaining non-marketed authorisations.

WP 5: Support Activities (p 136 – 149)

Page, line	**Comment**
Page 136	Whilst the EY report clearly acknowledges EMA's increased communication efforts, in particular via the EMA website and via other public communications, a third aspect of EMA's communication role should in our view also be reflected in the report as follows: • "EMA also plays a key role for the dissemination of important public-health communications within the EU regulatory network linked to EMA activities, by means of the Early Notification System and circulation of 'Lines to take' in order to help the EC and national medicines regulatory authorities to respond to external queries and to ensure that consistent and clear messages are provided to patients and health-care professionals across the EU in a timely manner."
Page 143	Under point 7.3.1 it notes that EMA makes use of Facebook to communicate, this is not the case.
Page 144	Figure 86, replace 'Facebook' by 'Twitter' and 'Multiple Twittter Feeds' by 'EMA Twitter Feed'

Page 138	"To measure and monitor the performance of Telematics services, additional indicators (such as incident resolution, data transferred between Telematics, volume of Telematics usage, etc.) are necessary. Moreover, the IT systems availability could be measured from an end-user perspective to report the perceived availability (such as time for an end to end process execution) more precisely.": Telematics performance is captured using indicators including availability in accordance with the service level agreement, times to incident resolution and service requests in accordance with the service level agreement, but also through customer (end user) satisfaction metrics which are collected through customer surveys at point of incident resolution.
P138, P139, P142	"Regarding interoperability and cooperation, interviews found that work is needed in order to optimise the use of SharePoint and/or database repositories highlighting the need to make telematics more user-friendly. Currently, the difficult user interface can at times prevent easy access to stored information due to information being stored in different tools and not easily transferable between areas. This was identified by stakeholders interviewed during case studies as a point of improvement related to knowledge management overall within the network, to address the need of effective access to information." "More specifically, experts and NCAs underlined the lack of tools that allow work to be undertaken horizontally on the same documents. A common IT SharePoint workspace could be developed for the centralised procedure in order to allow, for instance, rapporteurs and co-rapporteurs from the from the CHMP to work on the same document in parallel, such as for a joint assessment report." "Whilst the overall effectiveness of telematics can contribute to the efficiency of the system as a whole, the need to ensure that SharePoint and knowledge management are improved demonstrates the ability to improve the overall efficiency of the system. Some stakeholders have noted that the EMA telematics put in place may not be fully compatible with national systems, which can lead to a duplication in work and thus a decrease in efficiency." Concerns stated are being addressed with the implementation of a new regulatory processing platform which is enabling digital ways of working, better collaboration and a more secure way of exchanging information; it additionally bring together business processes and related data, including scientific information, that allows for business-process optimisation and better exploitation of knowledge by committee members, rapporteurs and others.
P143	"This points to a larger challenge pointed out by NCAs, namely consistency across databases. For Telematics to function effectively and to decrease the workload and increase efficiency, it is imperative that databases including similar data use the same datasets and vocabulary. 3 NCAs interviewed during the case studies have reported that this is not always the case."

	EMA along with its partners in the Regulatory Network has invested significant resource in defining common standards and vocabularies as a mechanism to ensure interoperability across applications (e.g. IDMP/FHIR, common vocabularies in RMS, common organisation list in OMS and the implementation of the SPOR programme.) Common technology, messaging and data standards are the way to achieve interoperability within the Network but to be effective these must be adopted by all partners.

Conclusions and Possible Actions (p 150 – 157)

Page, line	Comment
Page 151, Finding 3	See also comment on page 12: Action 3 highlights the need to allow CHMP focusing on more critical and complex applications. However, the need to focus scientific discussions on what is complex and critical is applicable to all of EMA's scientific committees. It is therefore recommended to reword this action by replacing "CHMP" with "scientific committees".
Page 153, Finding 11c	This states: "Finding 11c Databases are not functioning optimally, e.g. EudraVigilance". EudraVigilance meets all the business requirements adopted by PRAC and EMA Management Board and this has been confirmed by an independent audit and the EMA MB. Therefore, using EV as an example of a database not functioning optimally is factually incorrect and should be deleted. The EY statement is unsubstantiated yet given great prominence. EY should either provide robust evidence to support it or the statement should be deleted.
Page 154, Finding 13	See also comment on p 85. EMA does not consider that there is 'overlap or duplication' as early NCA and EMA advice are complementary. Moreover, coordination between EMA's ITF and national innovation offices is achieved through the EU Innovation Network (EU-IN).

Annexes (p 162 – 194)

Page, line	Comment
Page 167, table 13	A WP 2018 is publicly available for the BWP, SWP – see EMA website: https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp-working-parties-other-groups
Page 169, table 17	GEG: A workplan for this expert group is included within the CHMP work plan.
Page 170, table 17	Guidelines Consistency Group – Workplan "N/A" rather than "No"

COMMENTS FROM GERMANY

Accuracy consultation of Pharmaceutical Committee on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

Page, line	Comment
General comment	With regard to authorisations, only GMP inspections are mentioned and not GCP inspections that are also carried out. Likewise, among EMA Working Groups, the Inspectors' WG (PhV, GCP and GMP) are missing
Page 3	empty rows in the glossary should be deleted
Pages 6, 18	The CMDh is no EMA Committee
Page 7	It should read: The European Medicines Agency (EMA) was founded in 1995 and is a decentralised EU Agency, responsible for the coordination of scientific evaluation, supervision and safety monitoring of medicines in the EU
Pages 8, 50	"However, in areas that are currently developing and will gain more relevance…" should include also Infectious diseases, response to pandemics
Page 8	"Across the network, most NCAs have increased the resources allocated to EU level activities over the study period" should be complemented with "without an appropriate financial compensation"
Page 9, line 47	"…a majority of new, innovative medicines passing through the centralised authorisation procedure in order to be marketed in the EU." While formally correct, in reality all virtually innovative medicinal products are submitted in the centralised procedure.
Page 10	"The CP provides a solid and robust procedure, …; whereas the MRP and DCP allow country selection…" This wording suggests that MRP and DCP might not be solid and robust which is not correct.
Page 10, line 4	"…MRP and DCP allow country selection, where the choice for commercial and reimbursement decisions are generally considered." An additional important consideration that for the choice of the Reference Member State has been the (perceived) performance of the national agency.
Page 33	"Whilst EMA has developed mechanisms in order to facilitate the submission of applications for the centralised procedure, Directive 2001/83/EC does not set such steps for the decentralised and mutual recognition procedures. Nonetheless, it should be pointed that, as stated under Articles 17 and 18 of the Directive, Member States can take measures allowing the avoidance of double-applications in various Member States" The articles 17/18 have nothing to do with mechanisms for submission improvement. The paragraph needs to be corrected.
Page 38, lines 5-6	NCAs do not need to inform EMA when they issue a marketing authorization.

Page 38 „Conditions under which the procedure is conducted“	Commission's guidelines defining a "potential serious risk to public health" are set out in Article 29 (2) of Directive 2001/83/EC), not in Article 28.
Page 40, 4-5	As the text makes reference to the pharmacovigilance mechanisms set by Regulation (EC) No 726/2004, those are provided by Articles 21 (not 22) to 29 and the regulation as amended states that the provisions laid down under Article 104 of Directive 2001/83/EC (not 106). Maybe the authors have not used the current version of Regulation (EC) No 726/2004 under the headline "Pharmacovigilance mechanisms under the responsibility of EMA"?
Page 42 „Pharmacovigilance mechanisms undertaken at national level“	The obligation of the MAH to record and report suspected adverse reaction is stated in Article 107 Directive 2001/83/EC not in its Article 104.
Page 46, 10	As reference is made to Article 34 of Regulation (EC) No 726/2004, this Article is dealing with veterinary medicinal products.
Page 46 „Variations under the decentralised and mutual recognition procedures“	Regulation (EC) No. 1234/2008 is wrongly described with Regulation 1234/2008/EC (in the format of Directives).
Page 46, Minor variations	"After consulting other concerned authorities, the national competent authorities in the Reference Member State acknowledges that the notification received is valid." – "valid" should be replaced by "approvable".
Page 46, Major variations	"Once the applicant has submitted a request, the NCA of the Reference Member State acknowledge the valid application has been received. Within 60 days, the NCA must prepare an assessment report and a decision project, which will be forwarded to other competent authorities. Under certain circumstances the procedural timeframe may be reduced or extended up to 90 days. Within 12 days following the receipt of the report and the decision, the relevant authorities of concerned Member States will recognise the decision. Should a disagreement arise based on a potential risk to human health, procedures laid under Article 29 shall apply (Please refer to Referrals)." The RMS prepares no "decision project" but just the assessment report. Within 30 days following the receipt, CMS will recognize, not 12 days.
Page 47, extension applications	Last paragraph on EMA guidance should be deleted as this is a chapter on MRP/DCP.
Page 47, worksharing	"It allows an applicant to submit a group of Type B or a group of Type II variations, or a group of variations affecting various marketing authorisations." To be corrected to: "It allows the same MAH to submit a single variation or a group of variations affecting more than one marketing authorisation in more than one member state."

Page 47, grouping	"The grouping variation procedure is set under Article 7.2 of the Variation Regulation. It allows Market authorisation holders to submit multiple IA variations affecting either one or several medicinal products. Grouped variations must be distinguished from the workshare procedure. Although grouped variations can be subjected to the Work sharing procedure, as long as all medicinal products are affected by the same type of variations." To be corrected to: "The grouping variation procedure is set under Article 7 of the Variation Regulation. It allows marketing authorisation holders to submit multiple IA variations affecting either one or several marketing authorisations or several variations of different types affecting one marketing authorization in one single application. Grouped variations must be distinguished from the Work sharing procedure. Although grouped variations can be subject to the Work sharing procedures, as long as all medicinal products are affected by the same type of variations.
Page 47 (2.5.5 Sunset clause monitoring)	With reference to the provisions which contain the sunset clause it is the other way round: In Directive 2001/83/EC it is Article 24 and in the Regulation (EC) No 726/2004 it is Article 14
Page 47, SSc	"It should be stressed that the marketing authorisation remains valid if at least one presentation of the existing product is placed in at least one Member State". This is not correct for MRP/DCP. CMDh published guidance: "The individual MS will therefore need to take account of the specific situation for its own market. It should be noted that the application of the sunset clause is a national decision to be made by each concerned member state."
Page 68, line 17	"…as there is an equal distribution of CMS across Member States, there exists the potential to further distribute RMS". The Applicants choose the Reference Member State; a "distribution" by regulators in order to equal the distribution across Member States is not possible.
Page 80	Strimvelis: CAT was involved in consulting the national GMO authorities ~~Notified Bodies~~ on the Environmental Risk Assessment of the GMO
Page 91,line12-13	The involvement of external experts does not necessarily lead to a faster development of guidelines, but rather to a more reliable development of guidelines considering further perspectives.
Page 92, line 16	The number of compassionate use programmes performed in Germany is approx. 12-14 per year.
Page 99, line 4-5	Timeframes for MRP and DCP are published as flow charts on CMDh website. The timeframes are binding.
Page 99, lines 19-23	„Regarding the DCP and MRP, procedures are less burdensome for the system, though less transparent, predictable and efficient for applicants themselves due to inconsistencies and an unharmonised application

	of the regulation across MS. The current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases. " This view is surely not shared. MRP and DCP are very transparent procedures, informing the applicants about all steps during the procedure. The outcome is predictable if existing guidelines are considered in the application. The complete procedures are processed in an absolutely harmonized way, with the exception of some very few administrative national requirements that are well-known and published on the CMDh website. CMDh and HMA are continuously working on reducing these requirements which are all only concerning submission details but not the content of the dossier. Procedures are only delayed in cases where the published information is not regarded in the submitted documents. Only the national phase after finalization of the EU procedure is handled on a national basis.
Page 100, last paragraph	The numbers for MRP/DCP seem to be fluctuating in the same way as for CP. In figure 50 nearly the same curve is headed with "remained consistently high".
Page 111, paragraph on timelines	Single person's views should not be used in the final report. The overall timelines in MRP/DCP are well respected by the member states. It should be made clear that only the national phase might be handled differently by the member states. Innovations are furthermore not submitted via MRP/DCP but the CP is used.
Page 118, line 8-19	Proof of the quality, effectiveness and safety of the medicinal products must be guaranteed. The requirements for the granting of a marketing authorisation must not be neglected for generic medicinal products
Page 118, line 24-26	Same comment as above on page 99, lines 19-23, this summary and interpretation of MRP/DCP is not shared.
Page 118, line 27-30	The national requirements are published and well-known and reduced continuously with efforts of CMDh and HMA. Single examples should not be mentioned in this report and especially the case on individual equivalence studies is legally not correct and this is already reflected in published CMDh documents.
Page 118, line 31-42	It was always important for NCAs to keep the national responsibility for the legal status. Which status is possible in which MS is publicly available information, so should be no surprise for applicants.
Page 126, lines 1-2	It is not possible in MRP/DCP variations to "complete own assessment and procedure". The variation is a joint procedure with a common outcome, there is no room for "own assessment". Furthermore, the CMDh is especially promoting the use of the worksharing procedure in order to reduce national parallel assessments. As this is a voluntary procedure for the applicant but not the NCAs CMDh is using any opportunity to convince applicants of the advantages of the worksharing and encourage its use.
Page 126, line 6	It should not read "to update the variations" but "to update the variations guideline".
Page 126, paragraph on timelines	Usually the adaptation to the outcome of a safety referral is a type IA variation which is automatically started after receipt in the RMS or a type IB variation. A start date delay of 118 is surely an exceptional case.

	Most of the procedures are started according to the timeframes established. Most start delays occur due to invalidation issues because of incomplete variation application submissions. After finalization of the procedure the possible implementation date for applicants is written in the law, applicants do not need to wait for national approval longer than the timeframe stated in the regulation. They can immediately implement the changes.
Page 127,lines 13-18	The re-evaluation after five years should not be waived in order to ensure the best possible safety of patients.
Page 134, lines 1-5	The risk management system shall also include measures that may be taken by the national competent authorities to ensure the safe use of medicinal products where necessary. These measures would not be in place if the risk management system was not established.
Page 134, last paragraph	The new veterinary legislation is not yet implemented. Its success should be explored before it is recommended for other procedures. Furthermore, it is not correct that the data for variations not requiring assessment does not have to be submitted in addition to the common database. The current view of CMDv is that a submission of the eCTD sequences to NCAs is still necessary in order to keep the eCTD history correct.
Page 154, line 2	"Pre-submission procedures allow for refining applications and screening those that have little chance of authorisation at an early stage…" Screening is meaningless as validation of submissions is strictly formal and does not consider the scientific content; there is simply no mechanism that would allow the rejection of obviously premature submissions. There have been submissions apparently timed in a way that crucial data from the pivotal study would become available just in time for the response to the list of questions (or the list of outstanding issues).
Page 154, 155, finding 15 and 16	Add European Commission and CMDh to the relevant stakeholders (same applies for page 13)
Page 157, finding 23	The national requirements by single member states concern submission documents and are well-known. CMDh and HMA and the concerned NCAs are continuously doing all efforts to reduce these requirements.
Page 157, finding 25	The delay of procedure starts and restarts is not only a timeline question and not only related to MRP and DCP but is closely related to the quality of the submitted dossiers for both, CAPs and NAPs. Incomplete submissions lead to invalidations and further requests. This topic has already been discussed and guidance is published as "HMA/EMA BPG on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines.
Page 185, line 10	Clinical Trails – should be Clinical Trials
Page 185, line 16	CMP inspection planning – should be GMP inspection planning
Page 191	Paul Ehrlich Institute (PEI) – should be Paul-Ehrlich-Institut (PEI)

COMMENTS FROM IRELAND

Accuracy consultation of Pharmaceutical Committee on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

Member State: Ireland

If necessary, ple**ase add additional rows.**

Page, line	**Comment**
Page 151, finding 3 in relation to the CHMP: *Envisage a way to reallocate 'CHMP time on more critical/complex applications and innovative molecules (like for instance CAR-T CELL). For instance, confirmation through writing, adaptation of CHMP agenda, etc'.*	There is a downside... MAH perception that not equal consideration given, particularly when negative or in a referral.
Page 152, finding 5 in relation to combination products: *'A task force should be created...'*	It is considered that changes will be required, in the area of combination products, to the legislation such as to the variations regulation with an increase in variation categories. More coordination needed rather than the creation of a task force.
Page 152, finding 6 in relation to EMA/NCA/HTA coordination.	Pricing and reimbursement of medicines is a national issue. A priority, or the likelihood of success metric on the proposal for MSs to transfer competencies to a central level would be helpful.
Page 153, finding 9 in relation to medicines shortages: *'First step might be the development of best practices*	Best practice guidelines have been published on the EMA website. Perhaps a suggestion could be to rephrase the section to capture the essence of progressing further on work to harmonise efforts at EU level, rather than suggest the development of best practice guidelines.

guidelines at a European level, which could incite the Member States to cooperate more closely on the issue'.	
Page 153, finding 9 in relation to medicines shortages: *The text 'awareness is relatively low'.*	Not sure what is meant by the reference to this text – please clarify.
Page 154, finding 12 in relation to scientific guidelines: *'A regular review requires additional effort from the CHMP'.*	The majority of the effort comes from the WP of the CHMP and the EMA.
Page 155, finding 16 in relation to variations.	Type IA variations need to be periodically reviewed. The variations legislation is probably the best framework globally - it is risk-based with clearly defined expectations. To our knowledge, no other framework exists in any other (ICH) region. Refer to discussions within EU ICH Q12 team.
Page 155, finding 17 in relation to SMEs.	Only those issues related to the procedural side of CAPs should be under consideration.
Page 156, finding 21 in relation to: **'**companies cannot refer to existing documentation in MAA'.	Legislation change needed. MA are stand-alone, so need for data to be present in the MAA and hence MA once granted.
Page 156, finding 22 in relation to SA.	Industry often obtain SA on multiple occasions for the same product.
Page 157, finding 23, in relation to the interpretation of EU legislation by the various MSs.	More specific examples are needed. GL, Q&A, etc are not legislation. There is only limited primary legislation i.e. 2001/83, 2004 etc. This requires legislative change, as only way to ensure complete harmonisation is by Regulation, not Directive.

Page 157, finding 25 in relation to MRP/DCP timelines.	Time lines are formalised in 2001/83 and other directive/regulations.

COMMENTS FROM FRANCE

Accuracy consultation of Pharmaceutical Committee on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

Member State: FRANCE

If necessary, please add additional rows.

Page, line	Comment
Page 154 (finding 15), page 13 (line 15), pages 133-134 (section 6.3)	**RMP for generic products - proposal for deletion** This is strongly not supported, for the following reasons : 1) We are often in the situation where no reference product is on the market and there are only generic products; in this case having generic products on the market without any RMP and any "reference" product/reference safety profile to refer to cannot be acceptable. 2) Moreover, with substitution, generic products are often more used than the reference product (patients more exposed to generic products) so authorise generic products without any RMP will not be adequate. 3) RMP for generic is often not exactly the same compared to reference product, risk minimisation measures are not exactly the same, for example, they are not subject to some PASS studies/specific obligations. 4) Incorrect/Misunderstanding: France does not understand the potential reference to European pharmacopeia regarding safety profile as the pharmacopeia does not address this issue. The monographs of pharmacopoeias cannot replace Risk Management plans (RMPs) that are intended to minimise risks for a given medicinal product and to foresee further studies to learn more about safety profile of a given medicinal product. 5) The obligation has been introduced in 2012 that a RMP should exist for all new marketing authorisations and it is a tool for the product's benefit-risk balance to be continuously assessed. 6) Alternative suggestion: The RMP for generic might be more simplified and a tool such as a RMP repository will be helpful to better monitor these RMPs.

Page 157 (finding 24), page 103	**OTC / prescription status differs across MS** It is to be noted that the creation of the EMA/CMDh task force on OTC products has led to some progress and fruitful discussions. Work should continue and trying to harmonise the criteria and categorization of product is still difficult taking into account the important difference in the MS' healthcare system (coverage health care, access to physicians, reimbursement systems…).
Page 123	**This means that if safety issues are effectively addressed at an earlier stage of the procedure, the need for referrals diminishes.** This analysis is questionable. While other procedures enable to detect safety issues, referrals are often the most adequate procedure to analyse complex/critical benefit-risk issues.
Page 157 (finding 25) & page 13 (line 25)	**MRP / DCP timelines are not always respected** Even if this is acknowledged that NCAs should continue the efforts to respect the timelines France would like to point out the increased number of industry's request for clock-stop extension and extension of validation period due to delay in responding to validation issues. In addition it is to be noted that prior to MRP (or repeat-use) procedure, it is often needed to perform variation(s) in order to update the dossier; these updates might be considered by industry as a non-respect of timelines as the start of MRP is delayed. We consider that these updates are necessary and might guarantee that the MRP will run smoothly and might avoid major objections from the CMSs.
Page 119, section 5.5.3	**Diverging views and unharmonised application of the legislation present an administrative burden for industry applicants in the MRP/DCP** *[….] "Half of CMDh experts consulted found that diverging approaches among Member States impact procedures. In the open responses, they specified that different national requirements were the main source of inefficiency. This was confirmed by the NCA survey, where 15 out of 22 NCAs agreed that divergences could pose an additional burden to some extent. In this regard, the implementation of a pilot work-sharing procedure in the assessment of Active Substance Master Files (ASMF) was welcomed by stakeholders of the generics industry as a procedure that eliminates duplication and increases efficiency. In the current system, when an ASMF is used in multiple procedures and/or Member States, it can lead to duplicate assessments and divergent decisions. The work-sharing procedure was implemented by an HMA Working Group and harmonises the assessment and reduces the associated burden. Whilst this procedure is not mandatory, its application is strongly encouraged, as it provides an efficiency gain." ….]* **FRENCH comment:** The above observation on different national requirements and divergent approaches even on administrative matters is well supported. Implementation of the ASMF worksharing has been an important step ahead with several beneficial aspects to all NCAs and EMA to further minimise multiplication of assessment of the same data. However due to the voluntary nature of the procedure, its take up remains limited even now the pilot phase has ended. In addition, there has been cases where the same version of a given ASMF has been

	subject to re-assessment by a MS, CMS in the first procedure but RMS in subsequent procedures. Therefore, efforts are needed to not only expand the scope of the procedure by rendering it mandatory for all EU procedures but also to strengthen the main goal of the procedure by finding necessary solutions for a better acceptance of an assessment already done by another MS unless a Public health concern may have been neglected by the first rapporteur.

FRENCH POSITIONS ON SUGGESTIONS / CONCLUSIONS – To be discussed at Pharmaceutical Committee level

Develop as much as possible the coordination between NCAs / EMA and HTA bodies. This can be done by building on existing initiatives such as EUnetHTA and expanding and promoting – page 96 (finding 8)

We support the efficiency gain of joint advices between EMA and HTA bodies

Simplify the Variations legislation in line with the simplifications done for variations concerning veterinary medicines. This would notably include allowing MAH to make Type IA variations directly in the databases, without passing via NCAs - Page 125 (finding 16)

Though we support the idea of simplification of variations however we do not agree at all to bring it in line with proposals made for veterinary medicines. The proposals made currently for variations to veterinary medicines go beyond the suggestions made previously by ROG that were focused only on type IA administrative variations.

The recent proposals for variations to VET medicines suggest a classification practically on 2 categories: those to be assessed (mainly type II variations) and those not to be assessed (practically all current IA, IAIN and IB). Before any change, there is need to reflect on the experience gained and to envisage a reconsideration of the variation classification along with conditions and documentation and subsequently proceed to a simplification.

A simple alignment with VET medicines is not considered the appropriate way forward for Human medicines subject recently to incidents such as nitrosamines impurities in Sartans leading to huge efforts from the EU network to mitigate the risks to the patient within referral under article 5.3. procedure and requiring careful attention to changes to Marketing Authorisations. This is an example not currently applied to VET medicines and therefore it is not agreed that the same simplification can be envisaged for Human medicines. Further, revision of the variations guideline for Human medicines should include principles of ICH Q12 recently adopted but not currently applicable to VET medicines.

To what extent are post-marketing authorisation procedures efficient? Do they avoid any unnecessary administrative burden? - Page 134, section 6.3.

*[….] "The third area where an efficiency **gain exists is the administrative requirements of variations. [….]** The recently drafted revised legislation on veterinary medicinal products provides a potential simplification that could also increase efficiency regarding human medicines. The new legislation foresees two types of variations, variations requiring assessment and variations not requiring assessment. For variations not requiring assessment, marketing authorisation holders need to record the change in the product database within 30 days following implementation. As the link is directly between the MAH and the database, the administrative burden of submitting documentation to the NCAs is no longer exists. Upon entry into the database, the competent authority still informs the MAH if a variation is approved. If the system proves to be successful, it could be adapted for human medicines as well, rendering the process of variations more efficient. If this is the case, the type of variations no requiring assessment would need to be exactly defined, requiring and overall update of the variation classification guideline, an issue that was also raised by the previously mentioned HMA ROG." […].*

FRENCH position: The need for simplification of the variation system is supported; however caution is recommended in the goal of simplification as target population of Human and Veterinary medicines differ and the same safety and efficacy aspects acceptable to animals may not be applicable to humans. Therefore, not exactly the same revised list of variations can be applied to Human medicines. In addition, the new VET legislation on variations is not yet in force and the corresponding database not in use and therefore no experience has been gained. There is need for a careful revision of the current variation guideline in the light of experience gained and recent quality incidents in the field of Human medicines.

Specific product - The system has difficulties handling products on the border of medicines and medical devices - Page 152 (finding 7)

This proposal is supported; there is a need for guidelines for specific products such as combination products (medicines and medical devices); it should be noted that the work has started with EMA and some committees (Q/A have already been published).
As additional example, EMA and CMDh have finalized a regulatory guideline on allergens products which are also some specific products.

Scientific guidelines are not always up to date, and thus slow to adapt to innovation - Page 12 (line 12), page 91, page 154 (finding 12)
The introduction of a shelf-life for guidelines is supported; the frequency of review of these guidelines should be established with caution.

Recent example: the EC/EMA guideline on Extension application versus modification (NtA guideline) created in 2003 has been updated only in 2019.

Review the necessity of renewals - Page 154 (finding 14), page 11, page 14 (line 14)

This point is fully supported and has already been communicated to EC by the CMDh – Since 2012 and the new pharmacovigilance legislation, there is no need for renewal anymore (NCAs have now some legal tools that can permit to review the benefit-risk balance at any time).

Patient involvement across the network has increased significantly over the study period, which is perceived as a strength of the network – Page 8
It is generally true, but patients are not a uniform block. While patient associations are commonly involved, victim associations (and maybe consumer associations) are rarely involved. This could lead to giving more weight to the experience/hope of the benefit of a medicine, rather than on its safety.

The scientific expertise is adequate to provide strong and credible opinions – Page 8
It is generally true, but the network lacks expertise on pregnancy/breast feeding. Although it is a major aspect of the benefit/riks of medicines, the EMA has no dedicated working group.

Further formalise selection criteria that are currently based on the discretion of the chair / executive director to allow greater transparency and predictability - Page 13 (line 14)
This should also apply to referral procedures, based on clear criteria. The list of the applicants to the position of rapporteur should be shared with the committee members, as well as the rational for the choice of the rapporteur(s).

Interpretation of EU legislation differs from one MS to the other. And MS are requesting additional information related to the national legislation leading to administrative burden for the applicants (for instance, forms differs from one MS to the other) - Page 157 (finding 23)

The above observation on different national requirements and divergent approaches even on administrative matters is fully supported. There is need to avoid administrative burden for the applicants each time EU processes, documents, etc exist and allow such a simplification.

Beyond the above, different interpretation of EU legislation and technical recommendations leads to obstacles in implementation of worksharing procedures such as ASMF WS with the main goal of avoiding the re-assessment of the same data. Efforts are to be made to strengthen such procedures by finding necessary solutions for a better acceptance of an assessment already done by another MS unless a Public health concern may have been neglected by the first rapporteur.

COMMENTS FROM THE NETHERLANDS

Accuracy consultation of Pharmaceutical Committee on EY Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

Member State: The Netherlands – Medicines Evaluation Board/Ministry of Public Health, Welfare and Sport

If necessary, please add additional rows.

Page, line	**Comment**
Throughout the report	The report refers to 'reliable medicines' without specifying what is meant. Please note that the term 'reliable' is not used in legislation.
General	The report does not provide any information about the use of CHMP peer-review.
○ Page 5 – line: "Finally, due to parallel studies being implemented, fees as well as the orphan medicine regulation were not included either." ○ Page 15 - line "The scope explicitly does not include fees due to a separate, parallel study being conducted on this issue."	The report is unclear with regard to what is included in the scope of the study. The evaluation of the Commission referred to here not only covers the orphan regulation but also the paediatric regulation. Further, page 15 only refers to the evaluation of the EMA fee system.
Pages 6 and 18 – line: "EMA Committees: The Study Team participated in the meetings of 2 Committees: CHMP, and CMDh."	CMDh is incorrectly labelled as 'EMA Committee'.
Page 6 and 18 - table row 'Interviews with stakeholders at EU and international level'	The indicated stakeholder groups in the middle and right column don't match.
Page 6 and 19 – table row 'Product Case Studies'	The numbers don't align. The middle column states case studies were performed on 20 products, whereas the right column states that these were done for either 22 or 23 (15+8) products.

Page 8 – line: "The number of staff experienced a slight increase from 711 in 2010 to 799 in 2017 (+12%, including contract staff and seconded national experts),…[…]…" Page 71 – line: "The number of EMA employees (not including contract agents and national experts)…"	It is unclear whether these figures include interim staff.
Pages 9 and 75 – line: "Orphan designations by COMP could be better aligned with CHMP decisions."	This might need revision: orphan designation are given much earlier than CHMP procedures and therefore these two cannot be aligned. What needs to be aligned and coordinated are the CHMP decisions on the therapeutic indication and the confirmation of orphan status at time of marketing authorization.
Pages 10 and 98 – line: "The CP provides a solid and robust procedure, which is preferred by research-based companies; whereas MRP and DCP allow country selection, where the choice for commercial and reimbursement decisions are generally considered."	The text suggests that MRP/DCP would be less solid/robust compared to CP. CP and MRP/DCP are in theory only directly comparable in situations in which MA is requested in all member states simultaneously. Especially during COVID pandemic and general situations of medicine shortages MRP/DCP have proven to be of of great added value in enabling targeted and fast availability of products in specific member states. Added value and flexibility of MRP/DCP compared to CP is also elaborated upon on page 102. In addition, please note that with CP the MAH can still decide in which Member States he will market the product.
Pages 10 and 99 – line: "Increased visibility of DCP and MRP timeframes would be welcomed given the high level of heterogeneity across MS. […] Regarding the DCP and MRP, procedures are less burdensome for the system, though less transparent, predictable and efficient for applicants themselves due to inconsistencies and an unharmonised application of the regulation across Member States. The current MRP process allows countries to have additional requirements and administrative controls, which leads to	The text seems to be in contradiction with the fact that timetables for MRP/DCP have been determined and are publically available. Chapter 4 of the Directive provides the overall timetable, and detailed timetables are publicly available on the CMDh website – next to best practice guidelines to which RMS and CMS are bound. The only difference in timing for marketing authorisation can occur at the national level after the EU procedure has been finalised. If the text instead refers to the adherence to the applicable timetables for the validation, clock-stop and/or national phase of the MRP/DCP and not the clarity of applicable timelines in general, then this should be specified.

procedures being delayed in frequent cases" Page 157 – Finding 25 MRP/DCP timelines are not always respected: "Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources of formalising and redefining timelines …[…]… Industry stakeholders have more clarity on timelines"	
Pages 11 and 120 – line: "Variations, although effective, come with significant administrative burden, as each variation requires a validation by an NCA. The high number of Type IA variations (around 3,000 per year) mean a simplified system would present significant efficiency gains." Page 134, Fig. 81 'Evolution of variations received' and line "this entails around 6,000 administrative processes per year…"	It should be specified whether the given figures only refer to variations for centrally authorised products or also nationally authorised products.
Page 13 – line: "Review to what extent the 22-day framework for the written consultation of the Committee can be shortened, taking into account the 10-day framework which works well under the accelerated assessment.	It should be specified that reference is made to the Standing Committee.
Pages 13 and 154 – "Potential action: Eliminate RMPs for generic products, creating the opportunity to refer to active substance profiles in the pharmacopeia."	Please add EC and CMDh as relevant stakeholders.

Pages 13 and 155 – "Potential action: Simplify the Variations legislation in line with the simplifications done for variations concerning veterinary medicines. This would notably include allowing MAH to make Type IA variations directly in the databases without passing via NCAs."	Please add EC and CMDh as relevant stakeholders.
Pages 13 and 157 – "Potential action: Increase the work towards harmonising definitions and categorisation of products across Member States. This could be facilitated through EMA adopting guidelines on European standards/best practices."	Could this be further elaborated upon? Additional guidelines may not solve the issue at hand.
Pages 13 and 157: "Potential action: Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources or formalizing and redefining timelines."	Please add more context to potential action – this is not primarily a timeline issue but related directly to the quality of the application dossier. Please also refer to HMA/EMA Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines.
Page 16 – line Q4.2 "Do post-marketing authorisation procedures contribute to a higher degree of health protection for EU citizens and affect product complexity?"	Unclear what is meant with 'product complexity'.
Page 19 – table row 'Limited number of interviewed stakeholders for some Member State analysis', column 'Mitigation': "Where information was missing, the study team relied on findings from case studies in similar Member States as well as from feedback from EU-	It should be specified based on which criteria Member States were considered 'similar'.

level actors to describe the relevant issue."	
Page 23 – column 'inputs'	PDCO and academia are missing. Also, it should have been specified what is covered by 'industry' (also CROs?) and 'NCAs' (medicine regulatory bodies, inspectorates, OMCLs?).
Pages 24 – 28, section 2.2.1	CMDh is not mentioned as one of the key actors of the network. Please note that CMDh is not a committee of the EMA.
Pages 26 – 27, information on NCAs	The description does not cover the work of inspectorates and OMCLs.
Page 26 – footnote 12: "In the Netherlands, there is one NCA for authorisation procedures, and one dedicated to pharmacovigilance."	There is no separate NCA for pharmacovigilance in the Netherlands – MEB is competent authority for both authorization procedures as well as pharmacovigilance. There is a separate competent authority for quality and manufacturing supervision (Dutch health care inspectorate) – similar to the situation in Poland.
Page 28 – Fig. 3	It should be specified which organisations are meant by 'other EU and international organisations'.
Page 28 - line: "Apart from national authorisations in each Member State, three different procedures can be used by applicants looking to have a product authorised in Member States of the EEA"	MRP and DCP are procedures leading to NATIONAL marketing authorisations. The 'national authorisations' referred to in the indicated sentence are in fact 'purely national authorisations' where a product is only registered in a single EU/EEA country. Hence, there are three procedures leading to national authorisations and one leading to a central (EU-level) authorisation.
Page 28 – line: "These procedures vary based on whether or not the medicinal product has already been authorised in a Member State, on the scale to which the product will be authorised at EEA level, on the type of product as well as on the involved authorities providing the required scientific assessment for the quality, efficacy and safety of the product."	The type of procedure chosen/mandatory for a particular product does not depend on the authorities involved. In fact, the authorities involved depend on the chosen/required procedure and, in the case of a national marketing authorisation, the Member States in which the company wishes to market the product.
○ Page 29, Fig. 4 table row 'Market authorisation procedure overview', table columns on DCP – line: "The Market Authorisation is granted by NCAs and notified to the applicants and the EMA";	In accordance with Art. 22(2)c of Directive 2001/83/EC, 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. Such provision is not included for authorisations granted through an MRP or DCP were no post-authorisation conditions or obligations are imposed on the MAH in accordance with mentioned articles. The text therefore seems factually incorrect – or are these sentences referring to reporting to the article 57 database?

○ Page 38 – line: “In accordance with Article 21, once the National Competent Authority has issued a market authorisation, it must take the necessary measures to notify the applicant as well as EMA”; ○ Page 38 – line: “The fact that mutual recognition has been granted is to be communicated to the applicant, the Reference Member State, EMA as well as all concerned Member States”; ○ Page 39 – line: “Furthermore, the applicant must communicate the application to EMA, specifying Member States where an application has been submitted, as well as the dates of submission and copies of market authorisations that already have been granted. The applicant should also draw EMA’s attention if the medical product is under examination for authorisation in any Member State”;	Further, in regards the sentence “[t]he fact that mutual recognition has been granted is to be communicated to the applicant, the Reference Member State, EMA as well as all concerned Member States” (page 38): please note that the RMS is the one reporting, not the one that needs to be reported to.
○ Page 29 – Fig. 4: table row ‘Market authorisation procedure overview’; ○ Page 38, section ‘Conditions under which the procedure is conducted’ – lines: “Articles 29 to 31 detail the procedure that has to be conducted should a disagreement arise between Member States in the context of a mutual recognition procedure” and “If the Member States do not reach	Referrals are not restricted to the MRP but are also started in case of a DCP were at the end of the procedure disagreement exists between RMS and one or more CMS in regards the B/R balance of the medicinal product. Referrals resulting from such disagreement in either the MRP or DCP are handled at CMDh level. (Only) if the referral cannot be resolved by CMDh, the case is referred to the CHMP. Further, an Art. 30 referral is a harmonisation referral where differences in labelling content have arisen between MS. These referrals follow from a list of products drawn up by the CMDh upon a proposal from the Member States.

an agreement, a number of referral procedures can be initiated, in accordance with articles 29 and following of the Directive (See sub section 2.5.3)":	
○ Page 29 – Fig. 4: 'Outcomes'; ○ Page 39, section 'Market Authorisation subjected to specific Obligations (Article 22 of Annex I of the Directive)' – line: "The authorisation has to be renewed after five years based on a consolidated renewal application" ○ Pages 42 – 43, section 2.5.2 'Renewals'	The text suggests that there is a difference with regard to the renewal of the marketing authorisation, validity of the marketing authorisation after renewal, the required contents of the renewal dossier and objective of renewal between products authorised via the MRP or DCP on the one hand or the CP on the other. This is not the case. Art. 24 of Directive 2001/83/EC and Art. 14 of Regulation (EC) No 726/2004 contain identical provisions, with the exception of references to the authorising authority (national competent authorities or Member States vs EMA or Commission) and legislative basis (Directive vs Regulation). More specifically, these articles provide that: 1. 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 (MRP/DCP) or Agency (CP)*. To this end, the marketing authorisation holder shall provide *the national competent authority (MRP/DCP) or Agency (CP)* 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 of the Directive (MRP/DCP) or Chapter 3 of the Regulation (CP)*, 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 (MRP/DCP) or Commission (CP)* 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.
Page 30 – line: "Only products that have already been authorised in a Member State through a national procedure are eligible for mutual recognition"	Please note that MRP and DCP also lead to national authorisations. What is meant in this sentence is the purely national procedure. Further, this information is incomplete. Also products that have been authorised in several Member States via an MRP are eligible for another MRP. Via this "second wave" MRP the product is registered in additional Member States. This MRP is known as the 'repeat-use procedure' (RUP).

Page 32, Box 1 – line: "…all relevant EMA staff, including CHMP and PAC members…" Page 77 on pre-submission meetings – Line: "The meetings, which take place 6 to 7 months before MA and include the procedure manager and the EMA product lead, were noted by…"	Members of EMA scientific committees are not EMA staff but European experts made available by the Member States. Pre-submission meetings are further attended by the relevant team of the rapporteurs. Note: PAC should read PRAC.
Page 33 - line: "Whilst EMA has developed mechanisms in order to facilitate the submission of applications for the centralised procedure, Directive 2001/83/EC does not set such steps for the decentralised and mutual recognition procedures. Nonetheless, it should be pointed that, as stated under Articles 17 and 18 of the Directive, Member States can take measures allowing the avoidance of double-applications in various Member States."	Interpretation of Article 17/18 is not related to pre-submission meetings. Therefore, the added remark seems out of place. In addition, 'EMA' and 'Directive' are not same-level elements and can therefore not be compared. In this light it is further to be noted that Regulation (EC) No 726/2004 also does not provide for pre-submission mechanisms, as is mentioned in the paragraph above.
Pages 33 – 35, section 2.3.2 'Other pre-submission activities of EMA'	PIP procedures (PIP application, waiver, deferral, modifications and compliance check) are missing.
Page 33 – line: "These activities are independent from the procedures eventually chosen by the future applicant"	This is incorrect. The activities mentioned are for CP products. For products to be registered via the MRP/DCP scientific advice is given by NCAs, and protocol assistance and AMTP classification are irrelevant in such case.
Page 33 - line: "In order to implement its obligations with regard to scientific assistance, EMA established the Scientific Assistance Working Party (SAWP) within the CHMP."	The statement is not corresponding to the regulatory documents: 15 December 2016 EMEA/CHMP/SAWP/69686/04 Rev 12 Product Development Scientific Support Department Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP) 'The Committee for Medicinal Products for Human Use (CHMP) and the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) establish the Scientific Advice

	Working Party (SAWP) as a standing working party with the sole remit of providing scientific advice and protocol assistance to applicants." Further, please note that 'Scientific Assistance Working Party' should read 'Scientific Advice Working Party'.
○ Page 34 provides that the CAT was established to assess whether a product is ATMP; ○ Page 79: "The CAT has two important tasks, classification and certification of ATMP."	The role of the CAT and interaction with the CHMP in case of ATMPs merits further analysis. CAT contributes to CP in terms of classification and certification but also in terms of scientific advice.
Page 34 – line: "The European Medicine Agency's Committee for Medicinal Products for Human Use (CMDh) drafts guidelines…"	'CMDh' should read 'CHMP'.
Page 34 – line: "EMA has provided a large number of guidelines, which can be broken down as follows: …[…]…ICH guidelines…[…]…"	ICH guidelines are not drafted or provided by EMA, although EMA experts and EMA WP experts are involved in the drafting process as are experts from other ICH regions.
Page 34, subsection 'Regulatory support for the development of medicines'	Funding and fee incentives are not 'regulatory support' but financial support.
Page 35, subsection 'Regulatory support for the development of medicines'	Orphan designation does not fall under 'regulatory support', although regulatory (and financial) support activities exist for orphan products. The orphan designation procedure is required in order for a medicine to be authorised as orphan medicinal product.
Page 35, section 2.3.2 'Other pre-submission activities of EMA', subsection 'Other support for the development of medicines': Quality by Design	Although EMA provides regulatory guidance in relation to Quality by Design, Quality by Design in itself is not a pre-submission or support activity of EMA and should therefore not be labelled as such. It is a systematic approach towards the chemical-pharmaceutical development of a product that is based on predefined product characteristics and enhanced product and process understanding and quality control by building risk-management methodology in the design, development and manufacturing of medicines.
Pages 36 - 37, section 2.4.1 'Centralised procedure'	This section lacks information on rapporteurs and peer-review as well as on the different scientific committees and their roles, responsibilities and interactions during marketing authorisation procedures. Further, whereas information is given on authorisation under exceptional circumstances, this section lacks information on conditional marketing authorisation and accelerated assessment.

Page 37, section 2.4.2 'Decentralised procedure'	The type of information provided in this section differs from that of the section 2.4.1 'Centralised procedure'.
Page 38, section 2.4.3 'Mutual recognition procedure'	Information on the repeat-use procedure (RUP) is lacking.
Page 39, section 'Market Authorisation subjected to specific Obligations (Article 22 of Annex I of the Directive)'	The title of this section should read Article 22 of the Directive, not Article 22 of Annex I of the Directive. Part II.6 of Annex I provides the grounds based on which an application in exceptional circumstances can be made.
Page 39, section 'Market Authorisation subjected to specific Obligations (Article 22 of Annex I of the Directive)' – line: "The package leaflet must draw the professional's attention to the fact that certain available data concerning the product have yet to be assessed and verified"	This is incorrect. All data available have been submitted and assessed as part of the authorisation under exceptional circumstances. Instead, the package leaflet draws the attention to the fact that data on which the marketing authorisation was granted are as yet incomplete.
Page 43 – line: "Safety-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) and then either by the Committee for Medicinal Products for Human Use (CHMP) or by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for nationally authorised medicines; All other referrals on human medicines are assessed by the CHMP only".	This is incorrect. Referrals arising from disagreement between RMS and CMS at the end of an MRP/DCP are handled by CMDh. Only in case no agreement can be reached by CMDh, the case is further referred to the CHMP for arbitration. Reference is made to Art. 29 of the Directive.
Page 45, on Type IA variations for centrally authorised products – line: "Within 30 days the Agency will take measures allowing to assess the notification (see below)".	Type IA variations are only validated, not assessed. This applies to variations submitted for centrally and nationally (MRP/DCP) authorised products. Please refer to Chapter II and III of the Variation Regulation.
Page 46 on Type II variations for centrally authorised products – line: "Once the applicant of the variation has submitted a	As is the case for nationally authorised products, and in accordance with Art. 16.2 of the Variation Regulation, EMA may also reduce the timeframe of a Type II variation having regarded to the urgency of the matter.

valid application, EMA must issue an opinion within 60 days. The time frame can be extended up to 90 days in certain cases."	
Page 46, on type IB variations for nationally authorised products – line: "After consulting other concerned authorities, the national competent authorities in the Reference Member State acknowledges that the notification received is valid."	The description of a Type IB variation is incomplete. After validation, the procedure is started and within 30 days the RMS has to issue an opinion. In case of an unfavourable opinion, the applicant has 30 days to respond. Upon receipt of the response, the RMS has to issue an opinion within 30 days. In case of rejection, the CMS and applicant are informed of the grounds for rejection. In case of a favourable opinion, all relevant Member States have to vary the marketing authorisation within the timelines given in Art. 23 of the Variation Regulation.
Page 46 – 47, section 'Extension of marketing authorisations (Article 19)';	First, extensions of marketing authorisations are not handled through variation procedures but shall be evaluated in accordance with the same procedure as for the initial authorisation (210 days), but this is unclear from the text as the section is merely listed under section 2.5.4 'Variations' without adequate/sufficient explanation. Second, extensions of marketing authorisations can equally be submitted for centrally authorised products (in the report, the information is only included under subsection 'Variations under the decentralised and mutual recognition procedure').
Page 47, subsections 'Work sharing procedure (Article 20)' and 'Grouping variations'	Worksharing and grouping of variations can equally be submitted for centrally authorised products (in the report, the information is only included under subsection 'Variations under the decentralised and mutual recognition procedure').
Page 47, subsection 'Work sharing procedure (Article 20)'	Worksharing can be applied if the underlying products belong to the same MAH.
Page 47, subsection 'Grouping variations' – line "The grouping variation procedure is set under Article 7.2 of the Variation Regulation. It allows Market authorisation holders to submit multiple IA variations affecting either one or several medicinal products."	The text incorrectly suggests that grouping can only be applied to Type IA variations. Instead, grouping of variations is also permitted in cases specified in Articles 7.2 and 13d.2 and in Annex III of the Variation Regulation.
Page 48 - line: "The annual reassessment process applies to authorisations that have been granted under specific obligations (Refer to 2.4.2). Such marketing authorisation covers product	A marketing authorisation under exceptional circumstances may be granted if the applicant can show he is unable to provide comprehensive data on the safety and efficacy of the product, not the safety and quality of the product. The quality data in all instances need to be comprehensive. Please refer to Art. 14.8 of Regulation (EC) No 726/2004 and Art. 22 of Directive 2001/83/EC.

for which the applicant is unable to provide the data required under Directive 2001/83/EC regarding the safety and quality of the product."	
Page 53 - line: "Standing Working Parties meet 3-6 times a year, with the exception of the SAWP, which meets 11 times a year."	Biologics Working party meets 11 times a year as well. It is advised to do double check the meeting frequencies of the working parties. In addition, the text is not in line with Table 13 on page 167 which provides the meeting frequencies of the standing working parties.
Page 53 - line: "There currently exist 8 SAGs of which one, the Inter-Committee Scientific Advisory Group on Oncology (IC-SAG), has specific RoP. All SAGs are linked to the CHMP with the exception of the IC-SAG, which works with all Committees except PRAC."	There is no SAG that is prohibited from working with PRAC.
Page 55 - line: "Whilst the issue was not brought up directly by the research-based pharmaceutical industry, it nonetheless mentioned that the coordination necessary to properly involve COMP in the authorisation procedures added an additional layer of complexity."	The need for early interaction and involvement of COMP in the authorisation process of orphan designated products is recognised. However, the last sentences in the paragraph (see quote) are not very clear, nor are the final message and recommendation.
Page 75 - line: "Orphan designations by COMP could be better aligned with CHMP decisions."	Not well specified recommendation as orphan designations take place much earlier than CHMP decisions (see also earlier comment).
Page 78 - line: "The SAWP has 36 members, including thee members each from the other three mentioned committees, COMP, CAT and PDCO. Its mandate is to provide scientific advice and protocol assistance, it coordinates the input and brings it forth to the CHMP. Its mandate, objectives and rules of	This is a conclusion based on the observation period of the study. The current situation has changed with SAWP having only 2 members from COMP, PDCO and CAT.

procedures are outlined in a specific document. 97% of respondents to the online survey considered the role of this entity to be clear, with the same percentage considering the activities of the SAWP to be appropriate and providing added value. All experts consider that the SAWP provides valuable advice to Marketing Authorisation Applicants, that if taken into account, makes the application process significantly smoother. Communication between the SAWP and other committees has improved over the study period, in particular, the increased exchange between COMP and SAWP as well as PDCO and SAWP was noted."	
Page 85 - line: "Room for improvement was identified in relation to pre-submission activities for the DCP and MRP"	The underlying source for this conclusion is not clear, but seems to be based on the survey responses as displayed in figure 34 on page 86. The questionnaire, however, does not seem to focus on pre-submission meetings for industry but rather on the dialogue between RMS and indicated CMS's prior to filing the application. In most cases such dialogue is not warranted as no pre-assessment takes place in MRP/DCP. The first question (guaranteed identical application files) is not up to Member States in any case. The onus lies with the company to make sure an identical application has been filed.
Page 85 - line: "Managing advice from various NCAs can be difficult for companies. For instance, where the requests are submitted in parallel and the outcome is not completely superimposable, complications can exist with a difficult implementation of different recommended approaches."	It is up to the company to request parallel scientific advice in several member states. The alternative route for companies is to request sole advice to the RMS.
Page 88 – Line: "The procedure presented a welcome opportunity to	What are MAPs?

reflect on how MAPs could be developed in the future."	
Page 99, section 5.1.1. 'Whilst the global number of CP applications has stayed constant, there has been a decrease in DCP and MRP applications'	It is unclear whether duplicate applications submitted simultaneously to the same RMS have been counted as individual MRP/DCP applications or as a single application.
Page 103 – line: "At the same time, the CP is more expensive than the MRP/DCP, especially if a product has multiple strengths."	This conclusion cannot be drawn for MRP/DCPs on average. This comparison can only be made for MRP/DCPs where all Member States are included. The total of all single fees charged by all Member States in an MRP/DCP will be higher than the single fee charged for a CP by EMA.
Page 115 - line: "Finding 1 There are instances where COMP has to revise Orphan indications following the discussions of CHMP 3.1.1 Organise structured exchanges between CHMP and COMP before the final decision on the indication is taken EMA secretariat Less divergences between different Committees / WP. An additional effort by the EMA secretariat is necessary."	To avoid such situations an early interaction is needed. Recommendation supported.
Page 116 – line: "In addition, benefit risk assessment decisions are made available to the public, as European Public Assessment Reports (EPARs) are available following the product authorisation. The assessments are of high quality, as confirmed by industry stakeholders and the product case studies and are adhered to by CHMP and PRAC."	In accordance with Art. 21 and 106 of Directive 2001/83/EC, public assessment reports are also made available for MRP/DCP.
Page 118 – line: "Currently, the Centralised Procedure applies the same administrative load to all types of procedures. This means that generics	In accordance with Art. 10.1 of Directive 2001/83/EC, the documentation required for generics is substantially less than for innovators as generics refer to the pre-clinical and clinical test and trial results available for the innovator/reference product.

require the same process, timelines and documentation as new and innovative products".	
Page 118 - line: "Administrative burden was identified by industry in relation to the DCP and MRP, particularly due to the diverging views that could be provided by Member States. For MRP/DCP, burdens can arise due to unharmonised interpretation and application of legislation. This makes procedures less transparent, predictable and efficient for applicants themselves due to inconsistencies across MS.	Diverging views on interpretation of legislation can occur both in CP as well as MRP/DCP. Cases at hand can be discussed in CMDh/CHMP. Furthermore, the reduction in numbers of CMDh referrals (see page 124) shows that in virtually all cases consensus is reached.
Page 118- line: "For example, the current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases. Another example is the case where a CMS may demand that the applicant demonstrates equivalence with other products on its own market, despite a European reference product existing."	This takes place outside the context of European procedure (for instance during reimbursement trajectory, related to substitution). If CMS files a request of this nature during MRP/DCP, it is denied as evidence of bioequivalence with the chosen reference product is sufficient. Text should there be read in correct context.
Page 119 - line: "The industry not adhering to timelines can pose an administrative burden for NCAs. There have been efforts at NCA and EMA level to set out voluntary best-practices, but so far, they seem to have little effect."	Please also refer to this notion in the executive summary as possible delays are not exclusively caused by Member States but (frequently) also by industry.
Page 125- line: "The distinction between the different types of variations is generally clear. However, at times, for the MRP/DCP there can be differences of	Quoted text is unclear – national variation is not possible for an MRP/DCP product.

interpretation between Member States, as confirmed by industry representatives. Instead of accepting the type of variation indicated by one Member State, some Member States prefer to complete their own assessment and procedure. This leads to a duplication of efforts and in the cases where two different conclusions are reached, additional burden for the MAH."	
Page 131 - line: "Per year, only a few signals lead to regulatory action, such as a referral, an update of the RMP or the requirement to conduct a study."	A change in product information as outcome of a signal management procedure should be qualified as a regulatory action – resulting in better product information which is available to patients and health care professionals.
Page 137 - line: "Whilst some Telematics such as the EudraNet or EUTCT are used throughout the whole procedure from research and development to publication, others are designed for a specific phase such as the Eudravigilance databases."	EV human is not limited to post-authorisation phase. Distinction between two modules should be made: EVCTM and EVPM. EVCTM is used during research and development, EVPM during post-authorisation and prior to publication.
Chapter 3 and further	In some instances it is unclear whether reference is made to MRP/DCP or CP or both and the report seems to put more emphasis overall on CP. The contents should be clear and balanced.
Chapter 5 and further	Whenever conclusions are drawn on the timetable for the CP, it should be made clear whether time between CHMP opinion and EC adoption is included or not. The text is not always clear on that.
Pages 162 - 163, Fig. 96 'Centralised procedure'	The timing of and activities during the clock-stops are not indicated whereas this has been done for the DCP (Fig. 97). Further, the CHMP peer-review is missing.
Pages 164 - 165, Fig. 97 'Decentralised procedure'	'National Competent Authority' should read 'Reference Member State', as was done for the MRP (Fig. 98). The flow-chart reads as if break-out sessions occur during every DCP whereas in reality these sessions are very rare. The flow-chart reads as if in all cases of no consensus a CMDh referral is started. However, a CMDh referral is only started when the RMS considers the benefit/risk (B/R) balance of the product to be positive whereas one or more CMS deem the product not approvable on the basis of a potential serious risk to public health (PSRPH). If the RMS concludes that the B/R of the product is negative, the product is

	deemed not approvable regardless of the opinion of the CMS on the B/R, since only a positive assessment by the RMS can be the reason for a CMS to raise a PSRPH concern. The flow-chart also implies that the national phase of the DCP normally happens after Day 275, whereas this is only the case if a CMDh and CHMP referral are required to reach consensus. Normally, the national phase starts directly after Day 210 of the procedure. General note: Fig. 97 should be corrected in line with the DCP flow-chart provided by the CMDh (June 2020, CMDh/080/2005, Rev. 4) and the CMDh Best Practise Guide for Decentralised and Mutual Recognition Procedures (February 2020, CMDh/068/1996, Rev.12).
Page 166, Fig. 98 'Mutual Recognition Procedure'	The MRP only has one round of assessment, not two. The procedure ends at Day 90 and is either directly followed by a national phase or referral + subsequent national phase. Any break out session usually occurs at Day 75, so within the procedure timeframe and not, as suggested by the flow-chart, after the end of the procedure. If no consensus has been reached by Day 90, the procedure is referred to the CMDh, which is not presented correctly by the flow chart. Only if the issue is not resolved at CMDh level the matter will be further referred to the CHMP. As already indicated above, the national phase of the MRP usually starts directly after Day 90. Only in case of a referral is the national phase delayed. This is not correctly reflected in the flow-chart. General note: Fig. 97 should be corrected in line with the MRP flow-chart provided by the CMDh (February 2020, CMDh/081/2007, Rev. 3) and the CMDh Best Practise Guide for Decentralised and Mutual Recognition Procedures (February 2020, CMDh/068/1996, Rev.12).