European Medicines Agency

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EMEA COMMENTS IN THE CONTEXT OF THE PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS: STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE

Overall, the EMEA supports the European Commission's legislative proposals to strengthen and rationalise the EU Pharmacovigilance System.

There are, however, a number of critical issues which require further consideration. They relate to areas such as:

- The establishment of the new Committee on Pharmacovigilance. Not only its positioning within the EU Regulatory System, primarily vis-à-vis the CHMP, needs to be further debated; the EMEA is also of the opinion, taking into account that with the current proposals the number of EMEA Committees in the field of human medicines regulation will amount to six, that an overall reflection on how these Committees can work together in the most efficient way is urgently required.
- The roles and responsibilities of all parties (EMEA, Member States and pharmaceutical industry) involved in the conduct of pharmacovigilance.

It is also very important that the consequences of the legislative proposals are carefully considered, in terms of the impact on (human) resources. As has already been shown in a survey performed by Heads of Medicines Agencies, resources at the level of the Regulatory Authorities are limited. Therefore, an in-depth impact assessment is vital in order to ensure that the objectives of the legislative changes can be adhered to.

The EMEA comments are divided in 3 parts (see attachments):

- Part I: EMEA Comments on the Key Proposals for Legislative Change.
- Part II: Detailed EMEA Comments on Proposed Legislation.
- Part III: EMEA Comments on the Impact on the Pharmacovigilance System for Veterinary Medicinal Products within the EU.

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PART I: EMEA COMMENTS ON THE KEY PROPOSALS FOR LEGISLATIVE CHANGE

Fast robust EU decision-making on safety issues by rationalising the existing EU referral procedures and reinforcing the Committee structure

1. The need to rationalise EU decision-making on safety issues is fully supported and many of the European Commission's legislative proposals should allow to achieve this aim.
2. The organisational structure to be put in place to allow for such rationalisation whilst further improving the quality of the scientific work performed should be able to address 2 objectives:

   - Provide the CHMP (which should be the sole EU Committee involved in the benefit/risk assessment of medicines for human use) with the best scientific expertise available within the EU to address current encountered difficulties and to meet future challenges. The availability of such expertise, which should advise the CHMP on safety related concerns, should enable to reinforce high-quality opinion-making at CHMP level.
   - Introduce the necessary arrangements to increase efficiency of operation within the EU Regulatory System network, and in particular its pharmacovigilance component, making best use of the available (limited) resources and avoiding duplication of efforts.

   The EMEA is of the opinion that the proposed EMEA Committee on Pharmacovigilance will not allow to meet the aforementioned objectives because of the following reasons:

   - As per the current legislative proposals there is a high risk of confusion as regards the scope of operation of both the CHMP and the Committee on Pharmacovigilance, not only in terms of unclear roles and responsibilities, but also with respect to overlapping activities (e.g. involvement in benefit/risk assessment). Divergences in opinion between both Committees, even if one Committee would report to the other one, and taking into account the proposed differential level of transparency on the outcome of the discussions, would be detrimental to the credibility of the EU Regulatory System and could result in a blame culture which would not be in the interest of public health.
   - Furthermore, the proposed scope of activities which ranges from scientific activities up to administrative (e.g. tasks in relation to PSUR coordination) will make it difficult for the most appropriate membership to be appointed. It would seem more logic to have a clear separation of scientific and non-scientific tasks and to allocate such tasks to the most appropriate fora.
   - In addition, the proposed organisational structure would lead to a further increase in the complexity of the scientific review processes managed at EMEA level and would be contrary to the spirit of simplification and rationalisation.

   In order to better cope with current difficulties and future challenges, the EMEA proposes:

   - To replace the proposed Committee on Pharmacovigilance by a "Medicines Safety Advisory Board" to be attached to the CHMP. Its primary role would be to advise the CHMP on any safety related aspects in order to support the CHMP in its benefit/risk considerations and its opinion-making for centrally processed applications/centrally authorised products and the referral procedures to be handled at CHMP level. The composition of such "Medicines Safety Advisory Board" should allow for the best

available scientific expertise within the EU (as opposed to the system of a representative per Member State), covering the various areas of expertise in the field of pharmacovigilance, and complemented with representatives of healthcare professionals and patients. All scientific tasks for centrally authorised products or products referred to the CHMP for review, currently allocated to the proposed Committee on Pharmacovigilance, should be taken on board by the "Medicines Safety Advisory Board". In addition to CHMP requests to the "Medicines Safety Advisory Board" for specialist advise on safety related issues, it would be highly recommended for the "Medicines Safety Advisory Board" to have the possibility to discuss on its own initiative emerging safety issues of which it has become aware, resulting, where relevant, in a recommendation to the CHMP that there is a need to further investigate the issue. This would allow the "Medicines Safety Advisory Board" to act as a forum where identified signals for medicinal products irrespective of the licensing route are discussed. For centrally authorised products this could result in a CHMP request to the Rapporteur to take the issue forward. For non-centrally authorised products this could result in a scientifically justified request from the CHMP to the European Commission for the initiation of an Article 31 referral procedure. This would not interfere with the possibility for a Member State to start an Article 101k procedure. In addition, the EMEA is of the view that it would merit to provide for a legal basis allowing centrally and non-centrally authorised products to be included into one single referral procedure when considered necessary (class effect). The EMEA would also recommend that there is a process of interaction between the "Medicines Safety Advisory Board" and pharmacovigilance inspectors.

- To strengthen the legal basis for the already existing CMD(h) by broadening its scope of activities to include regulatory, procedural and administrative activities on pharmacovigilance related aspects for non-centrally authorised products, such as PSUR coordination.

3. The need to rationalise the referral procedures for nationally authorised products and to provide for better implementation of agreed regulatory action at EU level is fully supported. One area of concern relates to the proposed concept of public hearings. Depending on the final directions as regards the organisational structure to be set-up (see point 2) and acknowledging the need for increased transparency it needs to be carefully considered if public hearings would be the most ideal tool to address the general public's concerns for more openness. It appears that the concept of public hearings is proposed to allow for "light" referral procedures (taking into account the likely high number of companies which could be involved) but this needs to be carefully balanced with the right for companies to defend themselves at the level of the CHMP and the level of interaction that will be allowed for the general public during such public hearings. Since public hearings usually only provide the possibility to the general public to be heard and to voice its concerns, it needs to be clarified if this would be the overall aim of the public hearings concept or if it is the European Commission's intention to allow for a debate to take place between the audience and the "Medicines Safety Advisory Board". Although the operation of public hearings can be addressed in a guideline, there is, however, a need to be very transparent as of the outset on the aim of such public hearings in order to avoid disappointment from the stakeholders when the new legal provisions are being implemented. The aforementioned right for companies to defend themselves at the level of the CHMP also needs to be taken into account.
4. The EMEA is of the view that there is a need to clearly indicate in the new legislation that the CHMP when considering regulatory action for a particular medicinal product (limiting or prohibiting its use) should also take into account during its scientific opinion-making the following aspects:

    - One aspect relates to the availability of alternative treatments across the EU. Availability of alternative treatments could increasingly become an issue over the next years, e.g. in the fields of orphan drugs, advanced therapies medicinal products.

- Another aspect relates to the fact that the CHMP scientific recommendation could create new public health issues (resulting from a shift from a no longer or more limited available medicinal product to other products, resulting in other safety concerns). Therefore, in such situations the wider perspective should be taken into account by the CHMP when considering regulatory action limiting or prohibiting the use of a product.

Clarify/codify roles and responsibilities and codify standards for industry and regulators

5. Overall, the European Commission's proposals in this area are supported since they should indeed allow for clearer roles and responsibilities for all involved parties.
6. However, certain roles and responsibilities could benefit from further clarification, as outlined in the detailed EMEA comments. This is for instance the case as regards the MAH's responsibilities in relation to the assessment of the effectiveness of the Risk Management Plan, since the MAH should be obliged to collect data and conduct studies on effectiveness as specified in the Risk Management Plan so that the Regulatory Authorities are in a position to assess such information. In addition, MAHs should be obliged to provide sales and utilisation data upon request.
7. The EMEA is also of the opinion that a legal basis should be introduced to allow the maintenance of long-term monitoring of exposed patients (through a legal obligation to the MAH), even after the MAH has stopped the marketing of the medicinal product or has ceased to exist and there is no transfer of the marketing authorisation to another company.
8. It would also merit to provide a legal basis for the EMEA to establish and maintain a European network of centres of pharmacoepidemiology and pharmacovigilance in order to facilitate the conduct of post-authorisation safety studies. Such task would be in line with the European Risk Management Strategy which has identified the establishment of a network of such centres to be an important pillar in the EU approach towards a more proactive conduct of pharmacovigilance, hence contributing to a further strengthening of public health protection.

Simplify informing the authorities about the company pharmacovigilance system

9. The EMEA agrees with the proposed legislative changes in this field which should provide for further simplification and rationalisation. However, some wording in relation to pharmacovigilance inspections requires further clarification as outlined in the detailed EMEA comments. The EMEA also proposes the establishment of a database, managed by the EMEA on behalf of the Community, whereby Member States would be required to enter pharmacovigilance inspection reports into such database (see also detailed EMEA comments).
10. In addition, it is proposed to introduce the concept of a risk-based pharmacovigilance inspection programme to ensure a cohesive and risk-based process of inspection and to avoid as much as possible redundant re-inspections and requests for assessment of the pharmacovigilance system master file during individual marketing authorisation applications.

Rationalise risk management planning

11. The concept of Risk Management introduced in 2005 Community legislation is a very important tool to have a more proactive approach towards the safety of medicines. Although the current proposals to rationalise risk management planning are overall supported, there is a need to introduce further changes. For instance, the dual terminology "Risk Management Plan" and "Risk Management System" should be

removed since it currently leads to a lot of confusion. There is only one system, the Pharmacovigilance System (company-specific), whereas a Risk Management Plan is product-specific. Hence, to call it a "system" is confusing. In addition, the European Commission's proposal to annex the Risk Management System to the marketing authorisation is not supported for various reasons (both matters of principle as well as practical issues; see also detailed EMEA comments). Instead, the EMEA proposes to annex the Summary Table of the Risk Management Plan to the marketing authorisation. Details of this Summary Table could be further specified in a guideline.

12. Although the concept of intensively monitored products is fully supported, the EMEA does not agree to replace the concept of a marketing authorisation under exceptional circumstances by a type of intensively monitored marketing authorisations with Risk Management Plans. The concept of a marketing authorisation under exceptional circumstances should be maintained to allow for those situations (e.g. advanced therapy medicines, orphan drugs) where efficacy data are likely to remain incomplete. In addition, it is proposed that provisions are made to allow the inclusion of any authorised medicinal product in the list of intensively monitored products, irrespective of the concept applied ("normal" marketing authorisation, marketing authorisation under exceptional circumstances, conditional approval) and irrespective of the time (pre- and post-authorisation), and to remove it from the list when the CHMP considers that it is no longer necessary. Furthermore, a refinement of the current legislative proposals is needed (see detailed EMEA comments) as regards the possibility for a medicinal product to be removed from the list. Also, the proposal for publication of such list of products under intensive monitoring is *in se* a good transparency initiative, however, there is a need for further clarification (see detailed EMEA comments).

Codify oversight of non-interventional safety studies

13. Although the legislative proposals in the field of non-interventional safety studies are welcomed, the EMEA is of the opinion that an impact assessment should be carried out to evaluate the consequences of the proposals. Since there are many non-interventional safety studies started every month, the workload imposed on the EMEA and the Member States will be very important.

14. There is a need to reconsider the definition of a PASS. A proposal for the revision of such definition is being finalised at PhVWP level and should be taken into account. There is also a need to apply a consistent terminology throughout the legislative text. Furthermore, a possible overlap with the supervision of interventional clinical trials in accordance with Directive 2001/20/EC, resulting in a duplication of work and possible confusion in the roles and responsibilities, should be avoided. It needs to be clarified if the intension of this revised legislation is to amend or to be complementary to Directive 2001/20/EC. It would be appropriate to have a careful check of the correct use of the terms "post-authorisation safety study", "clinical trial" and "non-interventional trial/study" throughout the legislation in line with their respective definitions.

15. Furthermore, it needs to be emphasised that there is a trend in society whereby Health Technology Assessment Bodies are increasingly asking for more evidence on the benefits of disease treatment. Taking into account such trend, combined with the current spirit of simplification and the need to reduce the administrative burden for pharmaceutical industry, there is a need to combine as much as possible further studies on safety and efficacy post-authorisation (cfr. also Article 14(1) of the recently approved Advanced Therapy legislation where it is specified that the applicant must indicate the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto).

Simplify and make proportional reporting of single serious adverse drug reaction (ADR) case reports

16. Spontaneous reporting has been identified in the European Risk Management Strategy to remain one of the cornerstones of the pharmacovigiloance system, whilst it has been recognised that there is a need to further improve it. Therefore, efforts which should allow to further strengthen the spontaneous reporting scheme are fully supported. This needs to be balanced with the necessary rationalisation in order to increase efficiency and avoid duplication of work. Important in such exercise is that the roles and responsibilities of all involved parties are carefully considered. The success of the current EU Pharmacovigilance System has been built on the balance between the EMEA, being responsible for the coordination of pharmacovigilance in the EU, and the Member States, being responsible and accountable for pharmacovigilance at local level towards their citizenship (patients, healthcare professionals and the general public). Any new legislative initiatives should focus on providing remedies for the identified weaknesses, whilst safeguarding the existing balance. Taking this into account, the EMEA:

    - is of the opinion that the reporting by healthcare professionals and patients as currently proposed will not be appropriate taking into account the Member States' institutional tasks;
    - does not support the proposed screening by the EMEA of medical literature. The EMEA is of the opinion that this constitutes a shift of the legal responsibility for a medicinal product from the MAH to the EMEA. The EMEA fully recognises that there is a duplication of work, but proposes that the work-sharing concept is applied at pharmaceutical industry level. The introduction of a public-private partnership with academia could be worth exploring in this field.
    - strongly recommends that the obligation is introduced both for the Member States and pharmaceutical industry to assure that adverse drug reaction reports of the highest possible quality in accordance with agreed standards are submitted to EudraVigilance. As the output of the EudraVigilance database highly depends on the input received, the EMEA believes that a clear legal reference would be beneficial to achieve this objective.
    - requests for further clarification as regards the responsibility of the EMEA and the Member States in the field of signal detection in EudraVigilance for all medicinal products, irrespective of the licensing route. Several articles in the legislation currently address this issue, but the proposals are not consistent.

17. The European Commission's proposal to broaden the definition of an adverse reaction is supported, but the EMEA is of the opinion that reactions after any use, including abuse, should also be captured. Therefore "and unintended" should be deleted in the definition. (see detailed EMEA comments for a revised definition). However, since there is a link between the definition of an adverse reaction and the criteria for suspending, revoking, withdrawing or varying a marketing authorisation, the EMEA would like to emphasise the far reaching consequences if for instance a revocation of the marketing authorisation would be (largely) based on reports on misuse and abuse. Please see also EMEA comment 24 on key proposals for legislative change as a possibility to address these concerns.

18. The Decision of the Council 2005/387/JHA on the procedure for Joint Action specifically mentions exchange of information on pharmacovigilance with the EMCDDA. The EMEA is of the view that such interaction in the field of misuse and abuse should be addressed. It is the Agency's understanding that currently such exchange of information is not taking place on a continuous basis.

Simplify and make proportional to risk periodic safety update report submission by industry (PSURs)

19. Overall, the European Commission's proposals to introduce a simplification in the management of PSURs, hence reducing administrative burden, whilst making the submission of PSURs more proportional to the knowledge of the safety of medicines, are supported in principle. As regards the proposed role of the Committee on Pharmacovigilance in relation to PSURs, please refer to the aforementioned EMEA comment 2 on key proposals for legislative change.

20. There is, however, one particular issue the EMEA would like to emphasise. It relates to the fact that PSURs are no longer required for certain medicines, unless it is a specific condition of the marketing authorisation. This proposal is supported in principle, as the experience accumulated over a large number of years has largely demonstrated that preparation and assessment of PSURs of old products or generic products by MAHs and Competent Authorities is not efficient and diverts human resources from more important tasks in pharmacovigilance. However, although it is acknowledged as stated above that pharmacovigilance activities should be proportionate to the risks and information needs for a product, there is concern that safety monitoring for established products could become a neglected area. For these products Regulatory Authorities would not receive updates and cumulative evaluation of the literature studies, although such information is very important (e.g. published drug utilisation studies providing information on new aspects requiring safety monitoring, such as the development of antibiotic resistance, new co-medication practices or other new use patterns). It is, therefore, proposed to introduce a new tool for these established medicines, i.e. a 3-yearly literature review from the MAHs, together with a scientific evaluation and proposals for update of the product information as necessary.

Strengthen medicines safety transparency and communication

21. The need to strengthen transparency and communication on the safety of medicines is fully recognised. The EMEA agrees with the concept of a European medicines safety web-portal but has a number of issues for further consideration (e.g. accessibility of the information to the public, maintenance of such information, etc) as explained in the detailed EMEA comments. In addition, it would seem appropriate for this initiative to fit within the more global picture of provision of information on medicines which is currently being established at EU level (e.g. DG Sanco's initiative on the establishment of an EU Health Portal).

22. The proposal for individual adverse reaction reports held on the EudraVigilance database to be requested by the public is supported but the consequences of this proposal should be addressed in the impact assessment carried out by the European Commission. For instance, it should be noted that current rules across the EU on transparency in relation to adverse reaction reports differ. This needs to be addressed in order to achieve a harmonised approach. However, this initiative relates to reactive disclosure of reports. The current responsibility for the EMEA to give (proactively) access to the public and MAHs to the EudraVigilance database is no longer foreseen. This should be reintroduced.

23. As already outlined in the aforementioned EMEA comment 3 on key proposals for legislative change, the usefulness of the proposed concept of public hearings is questioned. A proper impact assessment should be carried out.

24. Acknowledging the need to facilitate the rapid establishment of a EU reference database for medicinal products in order to properly conduct pharmacovigilance, the EMEA welcomes the legislative proposals made by the European Commission in this regard. However, the EMEA would like to point out that the proposed changes in Article 57(2) contradict with the current wording in Article 57(1) which states that EudraPharm should be updated and managed independently of pharmaceutical companies. Therefore, it is no

longer clear who has now responsibility for the content of the information (EMEA, Member States, pharmaceutical industry?). The EMEA, therefore, proposes to focus in the current legislative proposals on the need to identify medicinal products for pharmacovigilance purposes (e.g. signal detection, implementation of the EudraVigilance Access Policy) and to introduce a legal requirement requiring pharmaceutical companies to populate the EVMPD (EudraVigilance Medicinal Product Dictionary). The wording in relation to the EudraPharm database should, therefore, not be amended in the frame of this legislative review.

Clearer safety warnings in product information to improve the safe use of medicines

25. Although initiatives to have clearer safety warnings in product information to improve the safe use of medicines are fully supported, the EMEA strongly recommends that information on risks and benefits is balanced in the product information. Safety information on a medicine should not jeopardise therapeutic adherence. Therefore, provision of information on the risks associated with a medicine should always be balanced with information on its expected benefit. Consequently, the inclusion of a summary of key information about the medicinal product (not only with an emphasis on the risks; content of such summary to be defined in a guideline) is proposed. A reference to the importance (rather than making it an obligation which could lead to decreased compliance with reporting for other medicines) of reporting for medicines under intensive monitoring is supported.

26. Acknowledging the importance of both the SPC and the PL as the reference documents, there is also a need to completely reconsider, either in the context of the revision of the Pharmacovigilance legislation or in the frame of any future legislative proposals, how to better communicate with healthcare professionals and patients, not only taking into account currently identified difficulties, but also in view of a longer term strategy on information to patients and healthcare professionals.