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IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

SUMMARY OF THE REPLIES TO THE PUBLIC CONSULTATION

I. ABOUT THE CONSULTATION

A. INTRODUCTION

1. On 8 September 2011 the Commission launched a public consultation on a concept paper concerning the implementing measures in order to harmonise the performance of the pharmacovigilance activities provided for in Directive 2001/83/EC and Regulation (EC) No 726/2004.

   This relates to a mandate given by the EU legislator to the Commission with a view to harmonising the new activities introduced by the amended pharmacovigilance legislation.

2. The Commission is required, pursuant to Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004, to adopt several implementing measures covering the following topics:

   (a) The content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities, the European Medicines Agency (EMA) and the marketing authorisation holder;

   (c) The use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) The minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) The format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

   (f) The format and content of electronic periodic safety update reports and risk management plans;

   (g) The format of protocols, abstracts and final study reports for the post-authorisation safety studies.

3. Those measures supplement essential aspects of the new pharmacovigilance system with the more technical details that have to be observed by marketing authorisation holders, national competent authorities and EMA in the daily practice of applying the new legislation. It is therefore important that they are fit for purpose and strike the necessary balance between the fundamental objective of the current legislative framework for medicinal products, i.e. to safeguard public health, and general internal market requirements.

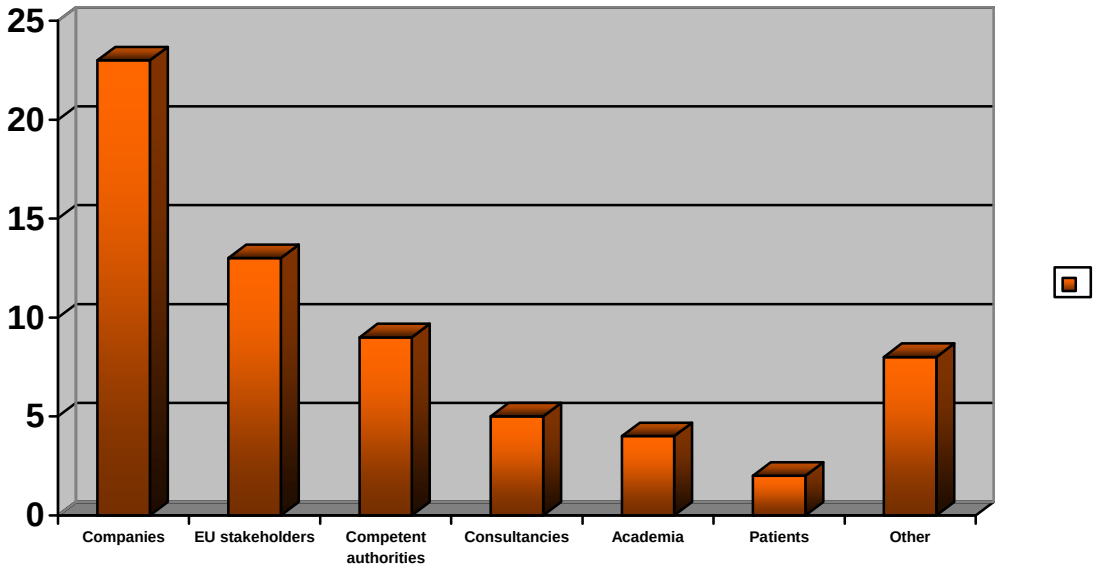
4. The purpose of the public consultation was:

- To seek views of stakeholders on concrete concepts in relation to the different topics to be covered by the implementing measures;

- To verify by means of several specific consultation items the apprehension of stakeholders in relation to additional features or underlying models.

5. In this context it was clarified that the concept paper itself was based on a detailed technical contribution that the Commission received from a dedicated project team of experts from Member States and the European Medicines Agency. This meant that it did not necessarily represent in all respects the position of the European Commission.

6. At the end of the consultation period on 7 November 2011, the Commission had received 64 responses, the vast majority of which came either from individual companies (23) or from stakeholder groups representing pharmaceutical undertakings on a European or national level (13). Nine responses came from national competent authorities ('NCAs'), ministries and agencies, including the European Medicines Agency ('EMA'), five from Consultancies, four from academia, two from patient representatives and eight from other entities and individuals.



7. On 22 November the Commission additionally held a stakeholder meeting in Brussels in order to give initial feedback on the public consultation and allow for additional comments on specific items that had been identified from the replies to the public consultation.

8. In accordance with the applicable guidelines, the responses have been published by the Commission.

9. This paper briefly summarises the responses to the public consultation document. In doing so, it not only reflects the majority views, but also tries to present a 'snapshot' of the range of responses.

10. This paper is in no way to be understood as an endorsement of any comment.

11. For the sake of brevity, the paper does not reproduce the consultation items or the detailed replies. Therefore, this summary should be read in conjunction with the consultation items set out in the concept paper as well as the published responses.

12. The public consultation is part of the ongoing preparation of the implementing measures. The information and views gathered in this way will be taken into consideration in the further drafting process.

B. GENERAL REMARKS

13. The public consultation was generally highly appreciated by stakeholders. It was noted that the level of detail provided gave a clear picture of the scope and allowed for targeted comments on the items covered.

14. In terms of substance, there was approval for the majority of general concepts, but particular requirements and features were commented on in some detail.

15. Some respondents criticised the decisions and requirements that are imposed by the underlying Directive or Regulation. However, as an implementing measure is framed by those basics acts and has to comply with and respect them, many respondents acknowledged that it cannot be used to modify any of the general concepts introduced by the new legislation.

16. Several respondents argued also that an implementing measure should be limited to high-level requirements, while practical details should be specified in the guidelines on Good Vigilance Practice. Others requested more precision, especially in relation to aspects concerning the format and content of some pharmacovigilance items.

C. PHARMACOVIGILANCE SYSTEM MASTER FILE

17. Practically all respondents welcomed the concept of replacing the detailed description of the pharmacovigilance system in every marketing authorisation by a Pharmacovigilance system master file, which is decoupled from individual marketing authorisations. However, many respondents criticised the amount of content requirements as foreseen in the concept paper. It was therefore suggested to have a critical look at all elements to ensure that the file would be succinct and that storage requirements are not simply duplicated in relation to existing documents stored at other places of a company. Some respondents argued moreover that the master file should concentrate on system description. Consequently, information on individual products should be limited. Many respondents favoured a modular content, if appropriate complemented by annexes, to facilitate maintenance.

18. In relation to the location of the master file several respondents saw difficulties arising if the location were to be linked to the place where the qualified person (QPPV) operates, especially for companies that work with a contracted QPPV. Additionally, some respondents suggested focusing more on electronic storage possibilities, potentially on servers that are not necessarily placed at the same site as the master file.

19. As regards maintenance, different views were expressed in relation to the requirement to notify significant changes of the master file to competent authorities. Several respondents acknowledged the usefulness of this, especially for the purpose of facilitating inspections. Other respondents feared that this would become a 'variation-like' requirement that would lead to unnecessary bureaucracy, especially if the notion 'significant changes' remains vague. Some respondents indicated that by means of the change revision history ('logbook'), which should be kept as part of the master file, authorities would have already a tool for easily tracing changes to the master file.

20. Different replies were also received as regards the requirement to keep copies of audit reports in the Pharmacovigilance system master file. Some respondents argued that such a requirement would not correspond to the basic act, which requires a marketing authorisation holder to keep only a summary note on the file and just until corrective measures have been taken. Others stressed that audit reports contain confidential data and/or may impair the impartiality of internal/external auditors or inspectors. On the other hand, some respondents welcomed the easy traceability of audit reports in the master file as it would provide for complete and historical documentation of the functioning of the pharmacovigilance system run by the specific marketing authorisation holder.

D. QUALITY SYSTEMS FOR PERFORMANCE OF PHARMACOVIGILANCE ACTIVITIES BY MARKETING AUTHORISATION HOLDERS, NATIONAL COMPETENT AUTHORITIES AND THE AGENCY

21. A large number of respondents welcomed the concept of quality systems and the details provided in the consultation paper.

22. As far as the quality systems for national competent authorities and EMA are concerned, some respondents highlighted the need for additional quality procedures, especially in relation to ensuring proper management of conflict of interest in addition to the requirements related to the independence of funds of the public bodies already provided for in Article 105 of Directive 2001/83/EC as amended.

23. Additionally, some respondents raised the issue of transparency and called for a more pro-active approach that should also be reflected in the quality system. It was for example argued that it would be beneficial if meeting records of pharmacovigilance sessions and committees were made public instantly. Moreover, it was suggested that competent authorities should be asked to report back to health professionals and/or patients on the follow-up to adverse drug reports that are provided by those persons, or at least to ensure transparent handling that allows for traceability.

24. As regards quality systems for marketing authorisation holders, the broad lines of the concept paper were endorsed by respondents as useful.

25. It was, however, argued that more emphasis should be put on the risk-based approach, on which the amendments to the pharmacovigilance legislation rely. Several respondents regretted that this approach was not fully reflected in the audit provisions, which in their current wording would require a full audit every two years.

26. Many respondents criticised the provisions on document retention periods as being not clear enough and partially not manageable on account of the long duration.

27. Some respondents suggested clarifying in the part on quality systems the role of marketing authorisation holders in relation to the detection of duplicates.

28. Other respondents raised the possibility of imposing on marketing authorisation holders additional quality procedures, especially in relation to communication with third parties, including patients and healthcare professionals, and reporting on studies.

29. Finally, some respondents discussed the possibility of differentiating within the detailed requirements for quality systems between different categories of marketing authorisation holders, for example in relation to producers of generics or herbal medicinal products. Some respondents felt that provisions should be less detailed for certain categories of marketing authorisation holders.

E. SIGNAL DETECTION AND RISK IDENTIFICATION

30. The proposal on monitoring of Eudravigilance and detection and management of changed or new risks was generally supported by stakeholders. More respondents requested further clarification of roles of the Agency, national competent authorities and marketing authorisation holders.

31. A need for a multidisciplinary approach to signal detection supported by statistical analysis has been identified; some respondents pointed to limits of routine use of statistical methods in relation to different types of medicinal products.

32. Additionally, respondents asked for clarification of frequency of monitoring proportionate to identified risk, of the validated signal and of the qualification of a signal for transmission to the PRAC.

33. Positive responses have been received on the extension of worksharing to all medicinal products. To mitigate risk associated with the concentration of all tasks in one Member State, well-documented decision-making, transparency and a peer review system have been proposed.

34. Need for an appropriate access policy in regard to Eudravigilance data and tools for marketing authorisation holders has been mentioned.

35. Importance of signal detection at national level has been highlighted by some respondents.

F. USE OF INTERNATIONALLY AGREED TERMINOLOGY, FORMAT AND CONTENT

36. The respondents in principle agreed with proposed terminology, format and content.

37. A question has been raised regarding what should be done when a required term is not available and which parties are to be informed. In addition, consideration of

certain flexibility in terminology, either for specific types of products such as homeopathics or reporting patients, has been proposed.

38. Concerns have been raised in relation to the phasing in of formats and standards, and introduction of an element of flexibility around a fixed date as proposed has been suggested.

G. FORMAT AND CONTENT OF ELECTRONIC TRANSMISSION OF SUSPECTED ADVERSE REACTIONS

39. Practically all respondents expressed agreement with the core proposals related to electronic transmission of suspected adverse reactions.

40. However, several respondents pointed to the lack of clarity and potential overlap of definitions of off-label, abuse, misuse and medication error, and would prefer these to be included in a guidance document.

41. Other respondents sought clarification that only those events that lead to an adverse reaction (e.g. related to a medication error or occupational exposure) should be reported within the pharmacovigilance system.

42. A question has been raised in relation to the processing of personal data and standardised pseudonymisation has been suggested.

43. Additional comments have been received regarding provision of copies of the literature references, summaries in English and language and translation-related issues.

H. FORMAT AND CONTENT OF ELECTRONIC PERIODIC SAFETY UPDATE REPORTS AND RISK MANAGEMENT PLANS

44. Practically all respondents welcomed the core of the proposal on electronic Periodic Safety Update Reports. A need for alignment with the ICH draft E2C (R2) has been highlighted. Several respondents provided comments on the order of modules, and concerns were raised regarding repetition and duplication throughout the document or with a Risk Management Plan.

45. Many respondents pointed out that requiring the signature of a qualified person for pharmacovigilance for all Periodic Safety Update Reports would impose an administrative burden.

46. In relation to an estimation of patient exposure some respondents expressed concern regarding interpretation of the proposed text as mandating drug utilisation studies on all products.

47. A shared view is that a Periodic Safety Update Report should be submitted once to a central repository without sequences specifically for centrally or nationally authorised medicinal products.

48. Respondents agreed in general with the concept and modular structure of the Risk Management Plan. Several respondents provided comments on the order of modules and raised concerns regarding repetition and duplication throughout the document.

49. Some respondents shared their views on transparency of the Risk Management Plans, expressing preference either for publication of a summary of the Risk Management Plan only or for a complete Risk Management Plan available to the public.

50. The question of Risk Management Plan waiver or of its parts has been raised in relation to products with a favourable safety profile for which no additional risk minimisation measures are required.

I. FORMAT OF PROTOCOLS, ABSTRACTS AND FINAL STUDY REPORTS FOR POST-AUTHORISATION SAFETY STUDIES

51. Respondents agreed in principle with the proposed formats as covering the key requirements. However, many respondents considered this annex to be too detailed. Comments pointed out that the structure of study protocol, abstract and report should be modified to help the flow of information and should provide flexibility to address different types of studies. Preferences on the position of some sections have been expressed.

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