EFPIA/EBE/EVM proposals on the Revision of the Variations Classification Guideline

General

As a general principle, we propose the category of **minor variation of type IA** for any changes to the terms of the Marketing Authorisation that have **already undergone assessment** elsewhere by the relevant competent authority.

Pharmacogigilance

We understand that as part of the forthcoming revision to the Classification guideline, changes to accommodate recent developments in the Pharmacovigilance legislation will be introduced. We would like to take this opportunity to present our proposals for accommodating these changes.

1. In relation to the Pharmacovigilance legislation, the above-mentioned general comment would include a change in PSUR frequency or standard wording for Summary of Product Characteristics or Package leaflet, which have been determined following the consultation with the Pharmacovigilance Risk Assessment Committee.

2. With regard to the **introduction of the summary of the pharmacovigilance system** in the Marketing Authorisation dossier we welcome a pragmatic approach, allowing flexibility to pharmaceutical companies in determining their strategy and avoiding unnecessary administrative burden. We therefore propose the following:
   When done at the time of renewal, the introduction of the summary of the pharmacovigilance system must be integrated in the renewal process.
   It is welcomed that the Commission foresees the possibility of introducing the summary of the pharmacovigilance system on a voluntary basis at an earlier stage. In this case the Commission requires the submission of a variation request [*Reference: Commission Questions and Answers on transitional arrangements concerning the entering into force of the New Pharmacovigilance Rules published in February 2012]* and that further details have been published by the EMA and HMA *[EMA/HMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012, 23 May 2012*]. We note that the category of variation for introduction of the summary of the pharmacovigilance system has yet to be confirmed, but is likely to be type IA_{IN}. We propose the category of minor variation of type IA should be used instead, for allowing flexibility on when to submit the variation on a voluntary basis, depending on resources, budget or other practical considerations, particularly for MA where there is no DDPS currently included in the MA dossier.

3. We also note that the EMA/HMA Q&A that a 'one-off' grouped variation to introduce the pharmacovigilance system summary for all of the MAH's medicinal products across all the Members States is not possible. It would be preferable for a provision

to be made that allows for the **introduction of the summary** of the pharmacovigilance system for all medicinal products **simultaneously** (combining centralised and nationally approved products), at the choice of the MAH, following the same classification as indicated above.

4. In addition, the EMA/HMA Q&A indicates that **changes to the QPPV and/or QPPV contact details and/or to the PSMF location** will require the submission of a variation application. Although this information is unlikely to change very often, when it does change it will eventually impact all MAs held by each MAH. For companies with an extensive portfolio of products these variations will require significant resources and payment of fees across their portfolio that are disproportionate to the importance of the change and the assessment required. In the context of promoting better regulation, we believe that once introduced in the Marketing Authorisation dossier, changes of the elements of the summary of the pharmacovigilance system should not be seen as variations, considering that they are integrated as part of the maintenance of the Pharmacovigilance System Master File (PSMF). This includes changes to the location of the PSMF and the name and contact details of the EU Qualified Person responsible for Pharmacovigilance which must be submitted to EudraVigilance Medicinal Products Dictionary (EVMPD) in accordance with Article 57 of Regulation (EC) No. 726/2004.

Other considerations

In addition, we believe that the following three critical aspects should also be addressed:

- Provision is made for the introduction of a '**fast track' variation category** to facilitate urgent changes that need to be made in order to prevent drug shortages and maintain continuity of supply of critical medicines, e.g. changes in an API supplier.
  Shortage of drug products is becoming a growing concern for regulatory authorities, patients and healthcare providers. Disruption in the supply of medicines impact patients and clinicians directly and can result in interruptions of ongoing therapies, the use of alternative, or less suitable medications or even lack of medicines to treat patients. Whilst only singular cases of disruptions of the supply have been recorded in the EU, we believe every effort should be made to facilitate the introduction of suitable alternative supplies of medicines.

- Further consideration of accommodating **key elements of ICH Q8, Q9 and Q10 implementation**.
  We recommend that text is included in the guideline to clearly indicate that movement within a Design Space does not constitute a change that requires a variation to be submitted. Furthermore, the inclusion of more granularity in the Design Space classifications would be helpful.
  Also, consideration should be given to align the Variation guideline terminology e.g. minor and substantial/ major changes to manufacturing process with ICH Q8 terminology, for example, changes to non-CPPs and CPPs.

- Based on our experience, we believe it would be valuable to reconsider the classification for a **number of variation categories relating to biological/immunological products and substances** (i.e. either by removing the current excluding condition(s), or by downgrading the classification from a type II to a type IB or IA). In a number of instances there is strong scientific evidence that the changes have no impact on the Quality, Safety or Efficacy of the product, and therefore a comprehensive type II assessment process (as currently foreseen) appears disproportionate to the potential risks (obvious examples include minor

changes to manufacturing steps/equipment for finished products, minor changes to analytical methods, etc.). Pharmaceutical Companies specialized in the development and manufacture of biological/biotechnological/immunological products are currently gathering a detailed list of such examples with a clear description and science-based rationale for downgrading.

Implementation by Member States

Most member companies have experienced inconsistent application of the Classification guideline by individual Member States who have already implemented the Variation Regulation at national level. We would recommend that provisions should be introduced to **facilitate a consistent and harmonized implementation** of the Classification guideline, when the mandatory date for implementation at national level occurs in approximately 15 month's time.

Structure – CTD

The current structure and numbering system of the guideline is to a certain extent causing confusion, and a **structure referring to the CTD-Q sections** would be much more user-friendly. Therefore we would recommend that the Supporting Data/Documentation sections refer to the CTD-Q sections numbering system.

Further guidance

We believe that the ***development of a Q&A*** to clarify key points, not addressed by subsequent changes to Classification guideline, would be very beneficial.