SUBMISSION OF COMMENTS ON LEGISLATIVE PROPOSALS TO STRENGTHEN AND RATIONALISE THE EU SYSTEM OF PHARMACOVIGILANCE (5 DECEMBER 2007)

COMMENTS FROM EUROPEAN BIOPHARMACEUTICAL ENTERPRISES (EBE) – 1st February, 2008

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GENERAL COMMENTS

The European Biopharmaceutical Enterprises (EBE) supports the efforts on the part of the European Commission to strengthen and rationalize the EU system of Pharmacovigilance. We are pleased to see an acknowledgement of the significant administrative burden that some of the current EU PV practices create for Industry and also for competent authorities. We agree that a lack of harmonization of PV requirements among the Member States has led to complex and diverse reporting requirements for industry and we fully support the Commission's efforts to harmonize these requirements.

Overall, the consultation offers a number of excellent proposals that, indeed, may help increase the safe use of medicines and decrease the administrative burden for national competent authorities, the EMEA and the pharmaceutical industry, and these are welcomed. Centralized, rapid decision-making on safety issues should benefit patients and improve efficiency across all pharmacovigilance systems.

The EBE represents the manufacturers of biological medicinal products and would like to take the opportunity to draw the Commission's attention to certain areas where clarifications or changes are proposed which relate specifically to these products, and it is important to note that the term biological medicinal products is inclusive of both innovator products, as well as biosimilar products. Biological medicinal products are leading the way towards the future of medicine, which will include increasingly advanced therapies including cell-, gene-, nano- and convergence technologies. Our experience with biological medicinal products highlights the importance of improving the system of pharmacovigilance in order to be able to reliably detect uncommon, but important, adverse drug reaction such as immunogenicity related reactions and accurately identify the responsible product.

The EBE recommends that the commission consider ways of optimising healthcare professional reporting of adverse drug reactions as part of this process. This is particularly relevant given proposals to establish an intensively monitored medicines list at the European level, where reliance on healthcare professional recognition of these products is critical. It would be important to investigate the understanding of healthcare professionals about pharmacovigilance processes in Europe in particular.

Finally, the EBE has been actively working with other industry bodies and is aware of, and supports, the comments that have been submitted by EFPIA, which are focussed on more general aspects of the proposed changes. In particular the EBE supports the important concerns raised by EFPIA regarding proposals to release internal audit reports as part of the product master file, the public release of QPPV details, proposals to regulate phase IV studies and the need to ensure that harmonization of reporting requirements across Europe is achieved as a priority. We seek to be active participants in this process.

COMMENTS ON TEXT		
Precise Reference <u>and</u> page of consultation document	**Comment and Rationale**	**Proposed change**
Page 5 Section 3.2.4 Key Changes	For clarification, add 'agreed' to 'Ensure that the key risk management measures are included…' Risk management plans (RMPs) for all biological medicinal products, including innovator and biosimilar products, should address identified (i.e. during development or marketed experience) or potential risks (e.g. immunogenicity and class specific risks). The RMP should also appropriately reflect the volume of clinical data available at the time of approval. For example, a RMP for a biosimilar product should address plans to monitor product performance, including safety in the post-approval environment in recognition of limited data being available for this purpose pre-approval. This is particularly relevant with respect to uncommon but important risks, such as immunogenicity. Product identification is a key requirement to risk attribution and identification. To this end it is recommended that the commission address product traceability for biological medicinal products on a Europe-wide basis, rather than at national levels, as proposed by the Commission's services	'Ensure that the <u>agreed</u> risk management measures are included… Commission establish a task force to provide recommendations on how to address product traceability for biological medicinal products within a set period of time to enable risk attribution

Page 7 Section 3.2.6 Key Changes	The proposal to place a medicinal product on a list of intensely monitored medicines could provide important benefits to public health and safety if structured appropriately. For biological medicinal products the concept of an intensively monitored medicines list has particular merit given the differences between these products and small molecules. It is acknowledged that all new innovator products could be subject to intensive monitoring for scientific and medically appropriate reasons, and for durations specific to the product concerned. It is recommended that all biosimilar medicinal products be automatically added to the list of intensively monitored medicines for an appropriate period and on a product specific basis. It would be important to address the following for such a program not to have significant, albeit unexpected consequences 1. The perception in the mind of the prescriber that medications not on the list are safe and thus do not require monitoring, i.e., reporting. (and vice versa) 2. Stimulates reporting for those products on the list, leading to disproportionate reporting for those compared to others not on the list. 3. Rationalisation of reporting requirements processes to avoid confusion and duplicate reporting due to central, national and MAH reporting of the same event. 4. Clear criteria for inclusion onto an intensive monitoring program, and for removal from such a program based on product specific scientific assessment in consultation with the MAH	A detailed guideline with standard criteria for inclusion onto this list, and the period of intensive monitoring required; further guidance/clarity around how and when the list will be reviewed/maintained especially concerning the timing of products to be removed from the list should be developed. Language requiring harmonization of reporting requirements across Europe to avoid duplicate reporting Specific language requiring sharing of reports with the appropriate MAH to enable risk assessment Specific language providing procedural guarantees for MAH, including those to avoid any disclosure of any information or documents that may undermine the protection of the commercial interests of the MA holders and other persons (as required by Article 4(1) of Regulation (EC) 1049/2001) List of intensely monitored medicinal products should be consistent across Europe and members states should be discouraged from having their own list

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	5. Procedural guarantees for MAH, including to avoid any disclosure of any information or documents that may undermine the protection of the commercial interests of the MA holders and other persons (as required by Article 4(1) of Regulation (EC) 1049/2001) or their privacy.	
Page 8 Section 3.2.7 Key changes	Proposed changes to Article 101f of Directive 2001/83/EC should include a clause that exempts products approved via certain abridged procedures (such as small molecule generics) from the requirement to submit PSURs. It should be recognized that biological medicinal products are inherently more complex than small molecules and as such the exemption from risk assessment in the form of a Periodic Update Safety Report (PSUR) is not appropriate. Frequency of periodic reporting to be linked to the RMP	Biological medicinal products should be specifically excluded from this exemption.
Page 20 Article 101a	The need to ensure that biological medicinal products are clearly identifiable is fully supported. It is recommended that the Commission's services address proposals on how to ensure proper and clear identification of such products when prescribed and dispensed in the Member States (and the EEA countries). It is inappropriate and unfeasible for the member states to individually implement systems for product identification. There is a need for a European level solution to this problem, not only to address the needs of the current products, but in anticipation of the future availability of complex therapies in addition to biological medicinal products. The Commission should address such a need in this process, and given the complexities invite active participation from stakeholders such as member states, the EMEA, ENCePP, industry	We therefore suggest to delete the proposed Article101a of Directive 2001/83/EC and to replace it by an obligation for the newly created committee (to replace the existing Pharmacovigilance Working Party) to make concrete proposals, to be endorsed by the CHMP, in order to ensure the proper identification of all biological medicinal products in Europe within a defined timeline. This should include the requirement for the establishment of a public consultation process to provide recommendations for how to implement an European level solution

	associations and interested academic institutions. This group should consider potential recommendations such as the potential for unique identifiers (e.g. INN or alternate nomenclature systems) or alternate product identification strategies. It would be a natural and important role for the proposed new committee to replace the existing Pharmacovigilance Working Party to pursue the establishment of a European solution for this complex issue.	
Page 33 Article 101m	Collaboration/communication with third parties (including other major regulatory agencies, and the WHO) should be strengthened to make sure safety requirements are consistent on a global level and that tracking systems (naming, in particular) are not in contradiction inside and outside the EU. The proposed committee which will replace the PVWP should be responsible for engaging in harmonization discussions with other interested health authorities to ensure global harmonization of standards and nomenclature (e.g. INN, USAN) to facilitate effective global pharmacovigilance and risk assessment. This is not currently addressed in the proposals.	We therefore suggest adding an obligation for the newly created committee (to replace the existing Pharmacovigilance Working Party) to make concrete proposals, to be endorsed by the CHMP, in order to ensure the proper collaboration to pursue harmonization. This should include the requirement for the establishment of a public consultation process.
Page 34 Article 101p	The EMEA has recently clarified in a guidance document that a RMP is required in the following circumstances: "*With the application for a new marketing authorisation for:* *- any product containing a new active substance* *- a similar biological medicinal product* *- a generic/hybrid medicinal product where a safety*	Addition of the following text: *'1. In the case of medicinal products authorised -/-, the competent authority which granted the marketing authorisation may require a marketing authorisation holder to submit a risk management system if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. <u>This requirement should relate to the following:</u>*

	concern requiring additional risk minimisation activities has been identified with the reference medicinal product" (refer to EMEA/CHMP/96268/2005). This information should be added to the Directive.	*- any product containing a new active substance* *- a similar biological medicinal product* *- a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product* *Any requirement shall:* *(d) be made in writing,* *(e) provide a detailed justification…'.*