SUBMISSION OF COMMENTS ON THE EUROPEAN COMMISSION'S STRATEGY TO BETTER PROTECT HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE

COMMENTS FROM EUROPABIO – The European Association for BioIndustries / Stefanie Pingitzer

GENERAL COMMENTS

EuropaBio welcomes the opportunity to comment on the European Commission's comprehensive set of proposals which once implemented will have a very positive impact of the pharmacovigilance system in the European Union.
EuropaBio is the European Association for Bioindustries, solely and uniquely bringing together bioscience companies from all fields of research and development, testing, manufacturing and distribution of biotechnology products. It has 84 corporate members operating worldwide, 12 associate members and 5 BioRegions, as well as 25 national biotechnology associations representing some 1800 small and medium sized enterprises involved in research.

Healthcare biotechnology has already had a tremendous impact on meeting the needs of patients and their families, and will continue to represent the state-of-the-art evolution of science as applied to human medicine. Significant advances in biosciences and in manufacturing technologies have led to a steady increase of bio-pharmaceuticals and advanced bio-therapies that are depending on a regulatory framework that supports innovation.
The Biotech industry has extensive experience with manufacturing processes specific to biotech products and potential safety issues related to changing of production systems. We consider it as important to share our experiences and knowledge to develop adequate tools for managing risks related to adverse events emerging from specific conditions of the manufacturing of biotech products or the specific nature of such products and are ready to engage our efforts together with authorities and other stakeholders for a simplification, harmonisation, and transparency of the Community system. Those challenges have to be tackled in order to contribute to the efficiency of the systems, maintaining the safety of products in the market. The unique objective is to contribute safety of patients in the EU community system. Biotech companies recognise in terms of pharmacovigilance their public health responsibilities especially because they develop complex products.

We believe that the current EU pharmacovigilance system has important public health challenges where the industry is committed to deliver.
Duplication of efforts, insufficient transparency, new healthcare technologies to be delivered to patients and realisation of innovative European tools such as the EudraVigilance projects provide excellent opportunities to rationalize the current system.

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SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Section 3.2.4 Rationalise risk management planning Proposed Article 101p of Directive 2001/83/EC (page 34)	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 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. ATP requirements should also be introduced: As per Regulation (EC) No 1394/2007- Article 14: "measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto."	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 may relate to the following:</u>* *<u>- any product containing a new active substance</u>* *<u>- a similar biological medicinal product</u>* *<u>- a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product</u>* *<u>- an advanced therapy medicinal product</u>* *Any requirement shall:* *(d) be made in writing,* *(e) provide a detailed justification……'.*
Section 3.2.5 Codify oversight of non-interventional safety studies	Article 101h of Directive 2001/83/EC would prevent MA holders to "*initiate, manage or finance*" any "*non-interventional post-authorization safety studies*" where "*the act of conducting the study promotes the use of a medicinal product*." Clarification is requested as to whether the intent of the wording is	

[1] Where available

Proposed Articles 1(15) and 101h of Directive 2001/83/EC	only referring to studies sponsored by companies or whether the intent is to capture Investigator Sponsored Studies (ISS) as well. A company may financially support an ISS but have little or no control over many of the activities referred to in the sub-paragraphs of Article 101h. We fully agree with the Commission's services that safety studies should pursue scientific objectives and, in fact this is already a requirement. We nevertheless believe that pharmacovigilance and patient safety in Europe would be more appropriately enhanced by imposing a positive requirement to ensure that the act of conducting safety studies pursue a scientific objective, as opposed to the prohibition set out in the proposed Article 101h1.a). We also believe that imposing such a positive requirement will reduce the risks of different, or even potentially conflicting interpretations, at national levels. Under the current EPAR system, safety data generated in the post-marketing setting do not usually enter the public domain (unless the data in question require a change to the SmPC) – this is not consistent with the EU policy of presenting in the public domain (ie via the EPAR) a summary of core supporting data. EuropaBio therefore proposes additional transparency regarding post-marketing safety studies: • The EPAR issued at time of approval should more clearly list and give more detail on each Post Marketing Commitment (PMC) for a safety study or patient registry exercise. • Alternatively this information could be included on the 'intensively monitored' products website. • As each post-marketing safety study or registry is completed, a summary of the results should be added to the EPAR via a revision. Non-interventional studies requirements listed on article 101h are not very detailed, which could lead to major differences when implemented at national level (e.g. when do MAHs have to submit ISS). Furthermore the responsibilities of the MAH when financing non-	Amend text as follows: *Article 101h* *'a) ~~The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.~~ The studies shall pursue a scientific objective.'*

	interventional post authorisation safety studies will probably lead to a significant financing decrease of the ISS studies by MAH.	
Section 3.2.5	It is not clear what the qualifier "light" in "Light oversight" of post-authorisation safety studies means. Does this imply that the proposed level of oversight (described in pp. 25-26) is not as stringent as for clinical trials?	Remove the word "light" or replace it with a more descriptive term.
Section 3.2.6. Simplify and make proportional reporting of single adverse drug reaction (ADR) case reports, Page 7, first and second bullets	EuropaBio fully endorse the proposals which will serve to simplify ADR reporting. The changes will simplify reporting requirements and harmonise requirements regardless of authorising procedure.	
Page 7, Line 13	With regard to the proposal that patients and healthcare professionals should be asked to report all suspected ADRs, it is agreed that the requirement for patients to be asked to report is a new step right across the EU. However the legislative proposal currently contains no checks and balances to handle poor quality or malicious reports from patients or the means to flag the consumer source in the EMEA database as opposed to medically confirmed cases, to be able to compare and contrast observations from these separate sources. Further clarity around such safe-guards would be welcomed. We also recommend that safe-guards should be in place to protect personal data privacy.	Clear guidance for industry is needed on how to deal with patients' reports. Patients' reports should be verified by a medical doctor.
Page 7, 7th paragraph Literature screening	Scanning scientific literature on behalf of MAHs is an excellent initiative, but there must be a system for informing MAHs of new cases so that non EMEA compliance obligations can be met. Unless a rapid, robust and foolproof system is in place, all MAHs will be forced to continue literature screening in order to meet the	The EMEA could identify a list of local European journals for which it will take the responsibility to perform screening and rapidly alert MAHs of new ADRs. Industry should review scientific literature and report cases to EMEA. EMEA should enter case reports, avoiding duplication.

	requirements of ex-EU regulators. Some practicalities of this provision are not completely clear: How will MAHs get knowledge of or access to reports entered to Eudravigilance in the context of literature scanning? How to ensure that the screening is complete? Who is in charge of the assessment of findings? Who pays for this service, and how much? In addition, it should be noted that global biopharmaceutical companies will still need to perform such activities to meet the requirements of health authorities outside the EU. Therefore, an alerting process for the global literature may not be practical. Furthermore, even if industry would not have to report cases to EMEA, it would still be ethically obliged to review the literature on its products.	However, it has to be ensured that a provision is made for MAH access to or alerting of scientific literature for its drugs. It may be possible to establish a process whereby the EMEA could take responsibility for local European journals and <u>assign global literature screening to a single MAH.</u> In any case, if EMEA is in charge of literature screening, it should also be done in compliance with FDA requirements.
Page 7, Line 15 and proposed new article 101a	Whilst EuropaBio support the proposal to create a European list of medicines under intensive monitoring, we have the following comments and concerns: • Only products which have been granted approval subject to the criteria currently applicable for approval under exceptional circumstances (pursuant to the existing Articles 22 of Directive 2001/83/EC or 14(8) of Regulation (EC) No 726/2004) should be included in such a list, as opposed to products which have been granted a conditional MA or a "normal" MA or subject to other restrictions. • The impact of the inclusion of a medicinal product on such a widely publicly available list, including for the biotech companies concerned, should not be underestimated and should therefore be carefully assessed. • It is necessary 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). • Experience indicates that it is necessary to ensure full application of the well-established principles of proportionality and of equality of treatment when these	We therefore request the Commission's services to add to the proposed Article 100j of Directive 2001/83/EC the following: "*The Agency shall have due regard to the legitimate interest of marketing authorisation holders and other persons in the protection of their business secrets and ensure that inclusion and withdrawal of medicinal products in such a list and its maintenance and updating is done in a transparent and proportionate manner and that all stakeholders concerned have been actively involved in concluding/finalising the details of such proposals. The Agency shall not disclose any information or document were disclosure would undermine the protection of commercial interest of a legal or natural person, including intellectual property*."

	measures are devised. It is understood that one of the aims of placing medicines under intensive monitoring would be to increase reporting by healthcare professionals and patients of all suspected ADRs to these products. Creation of a European list of medicines under intensive monitoring per se is unlikely to achieve a significant increase in ADR reporting. It is therefore imperative that implementation of such a list is supported by appropriate and consistent measures / tools and educational activities across Member States. Further clarification on the reassessment of the RMP milestones with the view to remove products from the list of those intensively monitored would be welcome.	
Page 7, Line 14	With regard to removal of products from the list of those being intensively monitored, it is not clear who controls the decision to remove a product from the list and the process for communicating that a product has been removed from the list e.g. is this the remit of the Committee for Pharmacovigilance? It would also be helpful to have a clear target date for a first review of the status of a product.	
Section 3.2.7 Simplify and make proportional to risk periodic safety update report submission by industry (PSURs) Page 8, paragraphs 1 and 2	Proposed changes to Article 101f of Directive 2001/83/EC include a clause that exempts products approved via certain abridged procedures (such as small molecule generics) from the requirement to submit PSURs. However, biologicals are specifically excluded from this exemption. It should be explicitly confirmed in the legislation that all biological products will require a PSUR. As discussed above, biosimilars will be approved with a limited safety database and therefore safety data generated during the post-marketing phase will be essential to fully characterise the safety profile of these products. For this reason, pharmacovigilance in the immediate post-approval period will be of particular importance for biosimilars.	
Annex 1, Page 11, Line 11	The concept of unexpected ADR is removed. As the proposals apply to post marketing pharmacovigilance this shows a divergence from clinical trial definitions where suspected unexpected serious adverse reactions (SUSARs) was a key part of the Clinical Trial Directive.	The following definition of an unexpected ADR should be re-instated: *'Unexpected adverse reaction: An adverse reaction, the nature, severity of outcomes of which is not consistent with the summary of product*

		characteristics'
Annex 1, Page 11, Line 17	The proposal includes the suggestion that the definition of abuse of medicinal products is removed altogether with no new statement added. It is important to differentiate between adverse events resulting from wilful abuse of authorised medicines compared with medication errors. There is no definition yet provided of a medication error.	Add the following text: *'Adverse reaction resulting from abuse of medicinal products – intentionally excessive or unprescribed or illicit use of medicinal products by a patient or their associate, or intentional excessive or wilfully inappropriate administration by a healthcare professional to a patient, which may lead to harmful physical or psychological effects.* *Adverse reaction resulting from a medication error – unintentionally overdosed, incorrect or inappropriate administration of a prescribed medication or one mistaken for it, to a patient by a healthcare professional or by the patient or an associate, which may lead to harmful physical or psychological effects'.*
Article 1 (34), Page 12, Line 11	Great clarity is requested on the differences between the contents of the PVG system master file in comparison to the summary of the PVG system.	
Article 59, Page 19, Line 5	It is proposed that the package leaflet of products on the European list of medicines under intensive monitoring contains the key safety information about the medicinal product and how to minimize risks and that this information be presented in a black box. It is requested that the Commission consult with user testing experts to ensure that an appropriate layout and template is utilized for presentation of such information. Indeed before including such specific guidance in the legislation it might be useful to have carried out appropriate user tests. The legislative proposal suggests that the phrase "This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to ….". Such language may not be understood by patients or careers and might cause alarm. More patient friendly language should be sought and user tested. It is suggested that less prescriptive text be included in the Directive and that the details are left to guidance documents.	
Article 101a, Page 20, Line	The term 'doctor' has been used and it is suggested that it should be replaced with 'physician' in order to remove possible ambiguity.	*'The Member States shall take all appropriate measures to encourage ~~doctors~~ physicians and other health care professionals to report serious or*

11	Additionally, the use of the term drug reaction implies suspected therefore it can be deleted from the sentence.	*unexpected adverse reactions'*.
Article 101a, Page 20, Line 13	We fully support the need to ensure that biological medicinal products are clearly identifiable. We nevertheless regret that the Commission's services have not made any specific proposal on how to ensure proper and clear identification of such products when prescribed and dispensed in the Member States (and the EEA countries) and have instead left this issue to be addressed at national level. This could lead to numerous and potentially conflicting identification requirements being imposed at national (or even regional) levels. This potentially undermines the stated aims of the consultation document i.e to address the perceived "*lack of clear roles and responsibilities'* with respect to pharmacovigilance requirements and at introducing "*harmonisation of pharmacovigilance requirements among the Member States*", in view of the "*complex and diversity of the current reporting requirements*". Proposed changes to Article 101a of Directive 2001/83/EC include measures that require Member States to improve ADR reporting. Of particular relevance to the pharmacovigilance of biological medicines is the requirement that Member States *'shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable'*. In contrast to small molecule drugs, it is recognised that there may be clinically significant differences between biologicals containing the same INN. Consequently, it is possible that one biological product may be associated with a particular AE, whereas another product with the same INN is not. For effective pharmacovigilance for biologicals, therefore, it is vital that each ADR can be linked to a specific product, and not just to an INN. We believe that, this legislative proposal presents a unique opportunity to introduce a harmonised and uniform approach for ensuring clear and proper identification of biological medicinal products in Europe. There is a need for urgent regulatory action in	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 before the end of 2008.

	this respect since so-called biosimilar medicines have already been approved by the Commission, including biosimilar medicines that bear the same International Non-Proprietary Name (INN) as the innovator reference product. The above-proposed harmonized approach also fits well with the proposed creation of a committee (to replace the existing Pharmacovigilance Working Party) with clear responsibility for coordinating pharmacovigilance and for making recommendations on the safety of medicines to the existing Committee on Human Medicinal Products (CHMP). This committee could be entrusted with the responsibility of making proposals, with a sense of urgency, for the clear and proper identification of all biological medicinal products in Europe and for exploring potential solutions such as a requirement to prescribe such products by invented name only and a prohibition to prescribe them by INN. The invented name should be used for the purposes of safety reporting, particularly in the case of biologics.	
Article 101d, Page 22, Paragraph 3	The consultation includes the proposal to give the public access to individual adverse reaction reports held on Eudravigilance. Clarity is requested regarding the rationale, practicality and benefit of providing this information. The grant of public access to individual adverse reaction reports held on Eudravigilance should be made in compliance with the rules on public access to documents, including Regulation 1049/2001 (as required by Article 73 of the existing Regulation 726/2004).	
Article 101e, Page 22/23	This article proposes that reports of adverse reactions should be collated in one point within the community. Please could further clarify be provided as to what constitutes 'collating'. Will the collation occur via submission to the Eudravigilance database or does the marketing authorisation holder have additional responsibilities particularly with regard to adverse events occurring in third countries?	
Article 101e, Page 23,	For medically confirmed serious adverse reactions the MAH should submit electronically to Eudravigilance, no later than 15 days	Add the following text:

Paragraph 2	following receipts of the report. Expedited reporting should be limited to serious adverse reactions, with medical confirmation of relation, regardless of origin. Non-serious adverse reactions should be provided in aggregate reports and should be subject to monitoring and evaluation by the MAH in a reasonable time period.	2. *Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15 days following the receipt of the report, all serious adverse reactions that occur inside and outside of the Community and has been confirmed by a medical practioner'.~~all serious adverse reactions that occur outside the community.~~*
Article 101f, Page 24, Line 2	Guidance on an acceptable format for the new style PSUR would be needed.	
Article 101i, Page 27, Paragraph 1, Section f	It is questioned why it is necessary to make the list of the marketing authorisation holder qualified persons (QPs) for pharmacovigilance public along with details of the member state in which they reside. It is also necessary to protect their personal data and privacy. The EMEA and member states already have this information. The advantages of making this list public are not clear. QPs may become targets of animal right activist and their safety should also be of concern to the agency.	Delete the struck out text: *'……the Agency shall make public at least the following information…….* *~~(f) A list of marketing authorisation holder qualified persons for pharmacovigilance and the Member States in which they reside'.~~*
Article 101l, Page 33, Section 4f)	There is concern at the proposed requirement for the MAH to share internal audit reports with the Agency as this jeopardizes the audit as a tool for process improvements. Therefore the proposal to include audit reports in the PVG System Master File would only be possible if the file is only accessible to the MAH only.	Delete the text stuck out below: *….the Marketing Authorisation holder shall:* …… *~~f) Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices and place a report of the audit on the pharmacovigilance system master file.~~*
N/A	**Issues associated with product switching** As discussed above, because of the potential for clinically significant differences between biologicals containing the same INN, it is possible that one biological product may be associated with a particular AE, whereas another product with the same INN is not. For effective pharmacovigilance for biologicals, therefore, it is vital that each ADR can be linked to a specific product, and not just to an INN. Correctly identifying the cause of some types of ADR (eg where	EuropaBio believes that under some circumstances product switching (defined as changing treatment between different products with the same drug substance, which may or may not be initiated by the prescribing doctor) may have a negative impact on pharmacovigilance for biologicals. However, the potential impact of product switching on pharmacovigilance is likely to vary between different classes of biological medicine, and possibly between different indications for the same class. Any guidance on product switching for health professionals will therefore need to be specific to each product class and/or indication, depending on the nature of the product class and its clinical use, and on the associated risk factors for

	onset of signs is delayed) may be impossible where the patient has received several products, even with full traceability to the specific brands used. The true 'cause' of the ADR could be any one of the products used or indeed all of the products used. Moreover, it is possible that the act of product switching itself could be a contributory factor (for example, by triggering or exacerbating an immunogenic reaction). For this reason, frequent product switching may confound effective pharmacovigilance for biologicals. It might therefore be advisable to restrict product switching of certain classes of biological medicine (for example by advising that products for patients on long-term treatment should not be changed more than once every X months). The current proposals do not include any provisions that directly address possible pharmacovigilance problems specifically associated with product switching.	the effectiveness of pharmacovigilance. Nevertheless, it is important that any such guidance is consistent for each product within the same class and between Member States. For the reasons discussed above, therefore, EuropaBio believes that the current proposals, which are designed to improve pharmacovigilance in the EU, should include provisions to address the issue of product switching of biologicals. Because of the product-class specific nature of any guidance for health professionals that will be required, EuropaBio believes that the preparation of guidance for health professionals should be prepared following detailed scientific consideration by a suitably expert body, such as the Committee on Pharmacovigilance. EuropaBio therefore proposes that the legislative changes should include provision for the following: • That the Committee on Pharmacovigilance should examine the potential impact of product switching on pharmacovigilance of biologicals. • If it concludes that these are appropriate, the Committee should prepare product class-specific guidance on product switching for health professionals, with the aim of mitigating any negative impact on pharmacovigilance. • This guidance should be included in the product information (SmPC and perhaps also PIL, possibly in the proposed 'key safety information' sections) of each affected product.
N/A	**Parallel Import** In light of the amendments contained within this legislation it is important that the existing legislation and guidance covering parallel import and distribution are revised in order to ensure the highest standards of patient safety particularly with regard to product defects and recalls.	