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

COMMENTS FROM **EFPIA**/CONTACT PERSON Christine-Lise Julou

GENERAL COMMENTS

Need to strengthen, rationalise and provide legal certainty to the EU system of pharmacovigilance

Overall, EFPIA considers the draft proposals to be a valuable and important step forward in rationalising and simplifying the current European Pharmacovigilance System. We particularly welcome a number of initiatives such as the implementation of a Pharmacovigilance Master File, single point reporting to Eudravigilance **only** and electronic submission of. PSURs. However, a key issue resides in the uniform implementation across the EAA which will be absolutely critical if the desired end-point is to be achieved. Past experience suggests that there may be an imposition of additional national requirements such as continued direct electronic submission of ICSRs to some CA safety databases or individual requests for descriptions of the PV system in the affiliate of that country. This will not be acceptable as future local deviation merely replicates the complex, duplicative and unharmonised situation which already exists. Enforcement of submission to Eudravigilance alone throughout **all** Member States and a single PV System Master File will therefore be crucial or any benefit will be completely obviated. Where the foundation of the proposed legislation is the protection of the patient, striving for consistency through a single piece of legislation appears to be logical and would certainly allow industry to proceed with greater clarity, save time and deploy resources in a more efficient manner.

Committee on Pharmacovigilance

Replacing the Pharmacovigilance Working Party with a Committee on Pharmacovigilance is supported. However, it is important that the role and responsibilities of the Pharmacovigilance Committee and its interaction with the Committee on Human Medicinal Products are very clearly defined. For example, to be effective, and to protect the public, all pharmacovigilance decisions must be made on the basis of evidence-based science using transparent processes that involve input from all relevant stakeholders including considerations of both risks and benefits.
It should be made very clear that none of the responsibilities of the CHMP as currently outlined in Article 5 of Regulation (EC) No 726/2004 can be devolved to the Committee on Pharmacovigilance.

Qualified Person for Pharmacovigilance

Article 101i.1(f) (page 28) proposes that a list of MAH Qualified Persons is provided on a publicly accessible European medicines safety web-portal. EFPIA has strong objections to this proposal, for the following reasons:

1. The rationale for making QPPV details public is not clear and appears disproportionate – the QPPV acts as a single contact point for the competent authorities and the Agency on a 24-hour basis, <u>not</u> the general public. Therefore, who is the list directed at, and why?

2. It is a violation of the privacy of all QPPVs.
3. Public release of the identities of QPPVs has serious personal security implications and may expose QPPVs to unwarranted attention from individuals with harmful intent (e.g. animal rights activists). The personal safety of QPPVs should not be compromised by posting information that has no direct benefit to the public health.

We have no objection to the public being aware that each MAH has at its disposal a QPPV, together with their accompanying roles and responsibilities but the potential personal risks to the QPPVs in listing their names is not warranted at all. Hence, in this context, applicable directives on the protection of individuals with regard to the processing of personal data and on the free movement of such data should be re-considered and the potential consequences of this proposal should be re-evaluated.

Expedited notification of non-serious ADRs

Article 101e.2 (page 23) proposes that MAHs shall submit electronically to EudraVigilance all adverse reactions that occur in the Community (including non-serious ADRs) and all serious adverse reactions that occur outside the Community within 15 days of receipt. This proposal is ambiguous, and presents a major change in reporting obligations that will be impractical and create undue burden for industry and provide minimal benefit to the protection of public health.

Whilst EFPIA supports the requirement to submit all serious ADRs within 15 days of receipt, whether 'expected' or 'unexpected', thereby obviating the need to assess each ICSR against multiple national SmPCs for 'expectedness', it is not clear what public health benefit arises from imposing a requirement to submit all non-serious ADRs within 15 days of receipt. We can understand that these should be populated in EudraVigilance for signal detection purposes but it is not clear why expedited reporting has been extended to include non-serious reports that occur in the Community.

The proposal would present a major process change for MAHs. Many MAHs currently structure their case handling activities so that priority is given to case reports that require expedited notification. Consequently, it is usual for the data management of non-serious ADRs to take somewhat longer than serious ADRs, recognizing that (in general) non-serious ADRs have less impact for public health than serious ADRs. Therefore, it seems both unreasonable and impractical to impose a requirement that non-serious ADRs are notified within 15 days of receipt.

In addition, it should be clarified that this requirement only applies to non-serious 'spontaneous' post-marketing ADR reports that have been medically confirmed; otherwise, the legislation should clearly specify that it includes reports from consumers, if this is the intent. It should <u>not</u> apply to non-serious ADRs from clinical trials on marketed products, which are subject to Directive 2001/20/EC, or to non-serious ADRs from post-authorisation safety studies or other 'solicited' sources, which Volume 9A currently requires to be presented in their respective end-of-study reports. Extension of the process currently required for centrally approved products, namely periodic reporting of non-serious ADRs, should suffice.

Finally, considering that reciprocal requirements currently exist for competent authorities to notify serious ADRs to MAHs, this reciprocal requirement should be maintained with regards to the new provisions i.e. what industry has to send to the authorities should be reciprocated in terms of submission from the authorities back to the relevant MAHs. Therefore, the practical consequences for the competent authorities should also be borne in mind when considering the timelines for electronic notification of non-serious ADRs in the revised legislation.

Reporting adverse reactions that lack causality assessments

Although a brief definition of an adverse reaction is proposed in Article 1(11), this appears to be elaborated within Article 101e.1(b) (page 22), such that the definition of causal relationship proposed in this article is not wholly consistent with that provided within ENTR/CT3 (guideline supplementing Directive 2001/20/EC) which states the following: *The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship*. As proposed, it would encompass virtually all reports from all post-marketing sources (including interventional and non-interventional studies, and registries) that lack a specific causality assessment by the reporting physician (or patient)

i.e. it lacks any opportunity for the MAH to distinguish between (unrelated) adverse events and (suspected) adverse reactions in this situation. The article should be amended to allow the MAH to provide a causality assessment in such situations, thereby allowing for ‘unrelated’ adverse events to be excluded from a need for expedited or periodic notification. In addition, it should recognise the constraints that apply with regards to the collection of non-serious adverse events from post-authorisation studies and clinical registries, as currently recognised in Volume 9A. Proposed text is provided in the specific commentary on Article 101e.

Safety Communication and Transparency

For the sake of transparency and clarity, the information on medicinal products authorised in Europe (i.e. Eudravigilance, EudraVigilance and the newly proposed "safety web-portal") should be consistent and available on a single Community website.

Safety information must be provided in proper context i.e. an educational component is necessary to ensure that the concept of benefit-risk balance is well understood.

In due course the proposed presentation of information and the process for maintaining such information should be subject to stakeholder consultation.

It is suggested that information and assessment on a given medicinal product should be managed by the same Rapporteur or RMS to facilitate knowledge management.

Definition of Post Authorisation Safety Study

The proposed revision to the definition of a PASS in 2001/83/EC Article 1(15) (page 12) is too broad and remains open to interpretation.

Replacement of the phrase "…*in accordance with the terms of the marketing authorisation*…" by "…*with an authorised medicinal product*…" broadens the scope too much such that it could now encompass any study conducted post-authorisation, including clinical trials designed to investigate the safety and efficacy of new formulations or indications for a product that is on the market (i.e. new clinical development activities, ordinarily covered by Directive 2001/20/EC). This would create overlap and conflicting and/or multiple duplicative requirements, and conflicts with the notion that the definition applies to studies that relate to the authorised use of a product, clearly what is not intended by this proposed change. If the intention is to cover off-label use with a medicinal product, then this can be covered by the definition as proposed on page 38/109 below, with suitable explanatory text within Volume 9A.

The definition needs to be unambiguous. MAHs conduct various types of non-interventional studies once a product is authorised, many of which do not have an objective to investigate a known safety issue or to identify or quantify a specific safety hazard. For example, post-authorisation studies may be requested by individual regulatory authorities to address use patterns or health outcomes in relation to the particular public health system operational in that country, and the current definition and guidance leads to confusion as to whether or not these qualify as PASS. At present, there is confusion in many companies as to which studies should be classified as PASS. A variety of interpretations have arisen as a result of ambiguity in the definition, leading to outcomes ranging from inadequate company oversight of PASS, or non-inclusion of relevant studies in RMPs/PSURs, to inclusion of every post-marketing study and generation and reporting of data irrelevant to safety. MAHs are more likely to take the latter conservative approach, resulting in significant additional and often unnecessary work for both the MAH and the Competent Authorities. Therefore, a truly unambiguous definition is required – a suggestion is provided in the specific comments on Article 1(15).

Finally, the proposed legislation should clarify the scope of the requirements in relation to relevant studies conducted outside of the EEA (see specific comments on Article 101h – page 26).

Internal audit reports

Article 101l.4(f) (page 33) proposes that internal audit reports should be placed within the pharmacovigilance system master file. EFPIA considers this to be an unacceptable proposal, as such reports are confidential company information and there is no benefit to releasing them to an external audience. It should be sufficient to demonstrate that such audits are conducted; there should be no need to have to share the results with the competent authorities, given that they have their own capability to conduct inspection programmes to generate the information they need in this regard.

Hence, we strongly recommend that internal audit documents are not stored on the pharmacovigilance system master file. The reasons for preserving the confidentiality of audit reports include the importance of assuring that the MAH continues to have the ability to document self-critical findings and opinions as candidly as possible. Internal audit documents should be stored separately under specific procedures to protect the company's right to internal audit and recognize the confidential nature of the documents. Should a regulatory authority require access to company internal audits, a separate request process specific to these documents should be used. Instead, we would recommend that a description of the audit process is stored in the pharmacovigilance system master file, together with evidence that the company has an ongoing pharmacovigilance audit programme and that audits have taken place.

Inclusion of ADR forms within packages

Patient adverse reaction reporting forms should not be part of the patient information leaflet, as proposed in section 3.2.6. Given that the proposal has significant implications for manufacturing, distribution and storage costs, is there any evidence that such a system will increase ADR reporting from patients, provide better quality data or benefit the protection of public health?

Packs would need to be increased in size to accommodate insertion of an ADR form in addition to the current package leaflet. This would necessitate significant change to companies' manufacturing capabilities, presenting significant additional costs to the production of medicines, not lessened in any way by the multiple language requirements within the EEA. The increase in size of each pack would also result in additional transportation and storage costs for distributors and retailers.

In addition, there is concern that, by providing patients with ADR reporting forms in this way, healthcare professionals may feel less inclined to report ADRs themselves, knowing that the patients would now have this opportunity to report their adverse events to the competent authorities and/or MAHs. Also, although some patients are knowledgeable and provide clear reports, it must be recognized that patient reports can be difficult to interpret when evaluating the drug.

We suggest that more efficient (and possibly more effective) alternatives are considered, such as distributing the ADR reporting form separately from the packs or empowering patients to report side effects via toll-free company telephone numbers and/or company websites.

Submission of Periodic Safety Update Reports (PSURs)

With reference to section 3.2.7 the concept of 'linking' a ¨PSUR to risk management planning is welcomed in principle however it would be important

to precisely clarify how linking would work and to strengthen the proposal to the greatest extent possible to ensure uniform implementation throughout the EU. Applicability of the requirements regarding the submission of PSURs should not depend on whether a marketing authorisation was granted based on a certain application type (e.g. generic, herbals well-established, biosimilar etc.) but based on risk management considerations.

PSUR review for all products should be based on the Centralised Procedure review model.

Key safety Information

The inclusion of new sections highlighting key safety information needs to be given careful consideration. We believe that the Summary of Product Characteristics and Patient Information Leaflet should be revised rather than added to, so that safety information is presented in a clear and understandable manner.

Adding a new 'key safety information' section to the Summary of Product Characteristics and Patient Information Leaflet could be redundant with safety information provided elsewhere in these documents (e.g. Warnings and Precautions) and thus could cause confusion. It would be important to test the effectiveness of any new safety section to see if does not negatively impact the prescriber's and patient's understanding of the safety information. The required patient readability testing of patient information leaflets already documents the effectiveness of communicating important safety information to patients. If this new section is retained in the legislation, guidance should be provided on how this section should be written and define what comprises key safety information. It would also be important to communicate the benefits of a product and, in some cases, the risks of not taking the product.

Intensive monitoring

The proposal to establish a 'European list of medicines under intensive monitoring' raises a number of issues in particular in terms of perception by the different stakeholders. It is therefore imperative that the purpose and criteria for placing a medicine on the list are well defined and implementation is supported by appropriate measures/tools and educational activities to avoid reporting bias and non-compliance.
For different reasons, the addition of specific text on the outer box of medicines or in the package leaflet to indicate that a medicine is under intensive monitoring is not supported.
The rationale for concerns and suggested ways forwards are outlined in the detailed comments.

Acceptability of a Single Risk Management Plan

Risk Management Plans should be discussed and agreed without the need for multiple strategies and duplicative negotiations with individual Member States. Differences in disease epidemiology, medical practices or legal/cultural factors should not have an impact on the plan and may only result in a certain variation in the risk minimisation activities.

Authorisation under exceptional circumstances

The introduction of a clearer legal basis for post approval commitments should not be through removal of the option for an authorisation under exceptional circumstances which can be granted on very specific grounds set out in Commission Directive 2003/63/EC. As the current provisions have been applied in the case of important new drugs (e.g. for the treatment of HIV and sepsis), EFPIA believes that they should be retained.

SECTION 1 – INTRODUCTION TO THE CONSULTATION		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
All sections	We suggest that common terminology is applied throughout the document e.g. ‘risk management plan’ vs ‘risk management system’, and that you standardise references to the MAH (use 'they' rather than 'he').	

SECTION 2 – PHARMACOVIGILANCE AND BACKGROUND TO THE STRATEGY		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
	No comments received.	

SECTION 3 - LEGISLATIVE STRATEGY AND THE KEY PROPOSALS FOR LEGISLATIVE CHANGE		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 3 Section 3.1	Assuming the proposals to amend Directive 2001/83/EC and Regulation 726/2004 are adopted it is imperative to plan for corresponding amendments to the guidance presented in Volume 9A (last updated	Ensure that the proposals provide for resource to support amendments to Volume 9A in parallel with changes to Directive 2001/83/EC and Regulation 726/2004. Specify a timeline for the revision and publication of a

	April 2007). This is vital for both MAHs and the competent authorities as: 1. Volume 9A is tightly bound to the legislation which is to be amended, and 2. Volume 9A forms the basis of the documentation used for inspections.	significant update to Volume 9A.
Page 3 Section 3.2.1 Key changes	Replacing the Pharmacovigilance Working Party with a Pharmacovigilance Committee is supported. However, it is important that the role and responsibilities of the Pharmacovigilance Committee and its interaction with the Committee on Human Medicinal Products are defined. For example, to be effective, and to protect the public, the Pharmacovigilance Committee must be charged with the obligation to make all pharmacovigilance decisions on the basis of evidence-based science using transparent processes that involve input from all relevant stakeholders. In addition, its decision making capability should be on behalf of the whole of the EEA, and more effective in this regard than the current Pharmacovigilance Working Party. It would be helpful to clarify how the referral procedures for nationally authorised products are to be rationalized.	**Define** the role and responsibilities of the Pharmacovigilance Committee and it's interaction with the Committee on Human Medicinal Products. **Clarify** changes to the referral procedures.
Page 3 Section 3.2.1	It is important that industry is consulted whenever this committee is considering matters that may have practical implications for the conduct of pharmacovigilance by MAHs.	
Page 3	We are supportive of a stronger legal mandate of the	**Please clarify** the practical aspects of the new Committee:

Section 3.2.1	PhVWP as a new committee coordinating pharmacovigilance and making safety recommendations. That said, we note that this section refers to this committee making recommendations to the CHMP, whereas the draft revision to Regulation Article 56(1)(aa) suggests that the new Committee of Pharmacovigilance will have the status of a Committee under the EMEA equal to that of the CHMP and CVMP. How will this operate in practice?	• It would be important to clarify the decision making process and to which extent will the CHMP be involved in such decisions • What will fall within the scope of this new Committee? e.g. with reference to RMP reviews, signal detection, risk-benefit analysis etc.
Page 3/4 Section 3.2.1	We welcome the concept of restriction of referrals for national products, and new 'light' procedures and public hearings from a committee whose decisions will be implemented across the EU. That said, the term 'light oversight' or 'light procedures' is very vague, and the process around a public hearing is not fully defined.	**Please clarify** the intent/definition of the terms 'light oversight' or 'light procedures'. **Please clarify** the triggers for a public hearing; are they restricted to those mentioned in Chapter 6, Article 101k.1 a-e (page 29) and does this article only apply to national and Mutual Recognition or also Centralised products?
Page 4 Section 3.2.2	This will seemingly create a legal basis for a regulation on Good Vigilance Practice (GVP). However, we would appreciate a clearer outline of how (practically) this is planned and how it will be implemented and enforced. We suggest that GVP should be aligned with international standards per ICH E2D. Will this be the case?	**Please clarify** how the concept of GVP is to be implemented, and whether it will be aligned with the principles previously endorsed by the European Commission when they signed the ICH E2D guideline.
Page 4 Section 3.2.2	The EU PV system is based not only on the EU QPPV but also national QP's according to national laws and represents a more powerful network system. The different registration status of the products and accordingly the related responsibilities of the	**Amend to:** For the Member State competent authorities, EMEA 'including its committees), Commission and Marketing Authorisation holders including their <u>EU and national qualified persons</u> …

	stakeholders were completely removed from the text.	
Page 5 Section 3.2.2 Impact	With regards to the statement "*Clear roles and responsibilities will increase the robustness of pharmacovigilance which will drive innovation by increasing confidence and reducing costs and….*", it is unclear how "*clear roles and responsibilities*" will reduce costs. Subsequent texts should delete any reference to reducing costs in relation to this change.	**Amend to:** '*Clear roles and responsibilities will increase the robustness of pharmacovigilance which will drive innovation by increasing confidence ~~and reducing costs~~ and also supports earlier access…*'
Page 5 Section 3.2.3	EFPIA supports the concept of a simplified Detailed Description of the PV system and that of a PV System Master File, to be submitted on request or reviewed at inspection. We also welcome the proposal to have the PVSMF maintained on site. However, the requirements for the PVSMF need to be specified. Clear transition steps need to be detailed for authorised products, with a 'Detailed Description of the Pharmacovigilance System' (DDPS) previously submitted to a Competent Authority, for the change from the DDPS that is currently required to the PVSMF. It is proposed that a Type I variation or a notification letter be submitted to remove the DDPS from the dossiers for currently authorised medicinal products.	Specify the requirements for the PVSMF. **Add:** In the case of medicinal products authorised -/- [before the entry into force of this directive], the competent authority shall provide the marketing authorisation holder with an opportunity to submit a notification informing the competent authority that the Detailed Description of the Pharmacovigilance System (DDPS) is replaced by the Pharmacovigilance System Master File and that the DDPS will not longer be kept up to date as part of the said marketing authorisation.
Page 5 Section 3.2.3	It should be noted that the claimed simplification of the content of the MAA may have a compensatory increase in complexity for MAHs. If the phrase *on site* is interpreted to mean that a 'Pharmacovigilance System Master File' must be kept at each of the MAH's	The documents should either be submitted to the EMEA and made available to other Member State competent authorities directly from the EMEA, or it should suffice to retain a single file in the country where the QPPV's office is located or in the Member State where the main pharmacovigilance

	national affiliates, the overall effect would be to generate more documentation rather than less. Also, the first paragraph of 3.2.3 concerning the elements of the pharmacovigilance system to be submitted with the dossier appears to contradict the scope of the text on page 12, Article 8(3)(iaa).	system operates.
Page 5 Section 3.2.3	EFPIA does not support the proposal that the supervisory authority for centrally authorised products should be the Member State where the QPPV resides. Firstly, the QPPV person may reside in a different country than that where the main pharmacovigilance resources of the MAH in Europe are located. Secondly, the proposal assumes that the location of the company QP is static and that there is a constant organisational structure, whereas this is not the case with many MAHs. If the Member State where the QPPV resides becomes the supervisory authority for pharmacovigilance, a specific process would be required to allow for a change in supervising Member State if the company changes the location of its QPPV. Third, the proposal could present issues for companies when hiring QPPVs, particularly for small MAHs who outsource the QPPV role as they would need to insist that the QPPPV be located at one EU country for inspection reasons. Linking inspections to the QPPV location may also exclude people from becoming QPPVs when residing in the smaller/newer Member States.	**Amend to:** For centrally authorised products, create a specific supervisory authority for pharmacovigilance which is the competent authority of the Member State in which the legal entity of the MAH resides or the Member State where the main pharmacovigilance system operates.

	The supervisory authority should be tied to the pharmacovigilance system of the MAH, not to an individual, and it should recognise that the electronic age enables 'residence' criteria to be flexible for many individuals. Hence, we suggest that this proposal is amended to indicate that the Member State in which the legal entity of the MAH resides or the Member State where the main pharmacovigilance system operates becomes the supervisory authority for pharmacovigilance. This would appear to be more stable and less subject to change than the current proposal.	
Page 5 Section 3.2.3	The proposed legislation will probably have minimal impact upon the need for inspections of MAH pharmacovigilance systems, because of the current legal requirements. However, principals for harmonisation of inspection procedures and mutual recognition of inspection reports between member states and the Agency remain an important objective that has yet to be achieved.	
Page 5 Section 3.2.3	When it comes to implementing this provision, Volume 9A should be amended to explain how the supervisory authority for pharmacovigilance would work in practice and how it would benefit patients. Also, there should be an explanation of how the decision-making process for designation of the supervisory authority for the QPPV and PV System.	
Page 5	For clarification, please replace ‘key’ with 'agreed'.	**Amend to:**

Section 3.2.4		Ensure that the agreed risk management measures are included…
Page 6 Section 3.2.4	The legal basis for requesting risk management plans for authorised products should be clarified and included as an article in the amended directives.	Please clarify the legal basis for requesting risk management plans for authorised products.
Page 6 Section 3.2.4	*"The proposals could be cost neutral for industry and national regulators as the proposals should lead to a reduction in poor quality risk management plans and poor compliance*." should be deleted as it creates a false (and probably unsubstantiated) impression that MAHs create poor quality risk management plans and have poor compliance. Additionally, the proposals are not anticipated by industry to be cost-neutral as MAHs will have to run more studies, resource more monitoring and more inspections of both themselves and of clinical sites.	**Delete:** ~~The proposals could be cost neutral for industry and national regulators as the proposals should lead to a reduction in poor quality risk management plans and poor compliance.~~
Page 6 Section 3.2.4	The current legislation indicates that RM systems are requested where appropriate (See Directive 2001/83 Art 8). Here it indicates that "*risk management plans are only submitted when needed*".	**Please clarify** the scope of this requirement. Does it automatically extend to all well-established medicinal products?
Page 6 Section 3.2.4	We agree with the position that risk management plans (separate from the SPC) should be required only when they are needed. However, the associated guidelines should provide clear examples of when risk management plans are needed, to avoid any delay to the authorization process for new medicines.	In Directive 2001/83/EC, the split concepts in Article 8(3)(iaa) and Article 101p should be consolidated and the same language should appear in both places for clarity. In addition, language should be added to these articles that conveys unequivocally the intent of Section 3.2.4, such as: *"Risk management plans are only submitted when they are*

		needed."
Page 6 Section 3.2.4	Care must be given to the interpretation of "compliance" to RMP commitments, as in some cases every effort can be made to conduct a safety study but circumstances unforeseen by the MAH or authorities may make it impossible, for instance, to recruit within agreed timelines. Companies should be deemed in compliance if they can prove that all reasonable efforts were made to conduct the RMP obligations.	Introduce text to indicate that the focus should be on special commitments related to true public health issues with scientific justification, and that any requests for such commitments must be both practical and achievable.
Page 6 Section 3.2.4	With regards to the statement, "*These changes will be a major benefit to public health by ensuring that safety evaluation of products is prospective (i.e. based on risk management planning) and by ensuring that high-quality, EU safety studies are done (i.e. there is compliance) when justified by safety concerns.",* it is unclear whether this implies the need for safety studies to be conducted specifically in Europe. Certain safety issues may be more rapidly and sometimes better addressed with multinational studies including non-European countries or even conducted entirely outside of Europe. The limitation to Europe would not seem always scientifically justifiable if the patient population of interest is represented elsewhere and the safety concern is not dependant on medical practice.	
Page 6 Section 3.2.5	EFPIA agrees with the overall goal and rationale for the pharmacovigilance activities related to post-	**Please clarify** the definition of a non-interventional study, and refine the definition of PASS, as suggested in comments

	authorisation safety studies (PASS). Such safety studies should be high quality and should not be 'market seeding' studies in disguise. However, the definition of 'non-interventional' is not clear, and the proposed revised definition of a PASS in Article 1(15) is too broad. As written, almost all post authorisation studies could qualify as a PASS. The addition of *"characterising"* and *"or confirming the safety profile of the medicinal product"* are considered reasonable revisions to this definition. However, it is unclear why the phrase "*in accordance with the terms of the marketing authorisation"* is to be replaced with *"with an authorised medicinal product"*. The conduct of a study using a product authorised in the EEA in accordance with the marketing authorisation (e.g. dose, indication) is a prerequisite to any post-authorisation study, whereas the use of the term "*with an authorised medicinal product*" could be misinterpreted to suggest that studies using the authorised medicinal product, but in a different indication or using a different dose to that stated in the marketing authorisation, would qualify as PASS - these should be considered as phase IIIb clinical trials that should only need to be conducted in accordance with Directive 2001/20/EC. Consideration should be given to explicitly including in the definition that a PASS is conducted to address a specific safety concern and/or with safety as a stated objective.	on Article 1(15).

Page 6 Section 3.2.5	For non-interventional post-authorisation safety studies, the criteria for what constitutes "*promotional objectives*" and *'light oversight'* are not defined. What does "light oversight" entail? Submission of periodic reports? Approving the protocols? End of study reports? It should be clarified that for studies conducted in only one Member State that 'light oversight' would be conducted by that Member State. We are concerned that all non-interventional studies will be treated the same though they may be used for different purposes (e.g. a pharmacoepidemiological study of safety issues versus a market research study to help determine appropriate formulations are treated equally). Formal approval procedures for non-interventional studies should be put into place only when there is a legitimate and important safety question to be answered. It would be helpful to provide guidance on how reportable information from promotional programs will be handled.	**Amend to:** '*Light oversight (by EMEA pharmacovigilance committee ~~only~~ if* **the study is to be conducted** in more than one Member State; **by the Member State if the study is to be conducted to be in only one Member State)** *of non-interventional post-authorisation safety studies to ensure that they have health rather than promotional objectives.'* A guidance document with definitions including the definition of 'promotional' and 'light oversight', and describing which criteria are used to evaluate non-interventional post-authorisation safety studies should be developed. Guidance should be provided on how reportable information from promotional programs will be handled.
Page 6 Section 3.2.5	It would be good if the European Commission could take this opportunity of the legislation to clarify the definitions of interventional and non interventional studies, and solicited versus unsolicited reports.	
Page 6 Section 3.2.5	Concerning the legal mandate for PASS studies, how will this ensure that commitments made by the MAH at the time authorisation are honoured?	

	For example, if PASS studies fail to get off the ground due to low recruitment numbers, it is difficult to envisage how such a position can be recovered. There should be a pragmatic response to PASS studies that do not achieve the stipulated goals. In many cases recruitment targets can simply not be achieved if the anticipated market share is not achieved.	
Page 6 Section 3.2.5	In association with the implementation of risk management plans, a greater number of post-authorisation safety studies have been requested by regulatory authorities or proposed by the MAHs. This reinforces a need for effective harmonization across member states and requirements of improved assessment of quality and validity of study protocols, something that is sadly lacking at present.	
Page 6 Section 3.2.5	It should be made clear whether the PASS requirements apply to non-interventional post-authorisation studies being conducted solely outside the EEA. As proposed in this draft legislation, it seems that all protocols will require pre-approval. However, the provisions should exclude those studies which have been required by another non-EU agency such as the FDA - it would be very difficult to manage the situation where a study has been agreed with the FDA as a condition of approval in the USA only to have to tell them that some EU Member state wants a change to the study protocol.	

Page 6 Section 3.2.5 And Article 101g/h Page 26/27	We have practical concerns about 'PASS' studies requested by agencies other than the competent authorities, such as pricing authorities, or conducted by third parties such as physicians and academic institutions. Industry is usually obliged to provide some support/sponsorship to such studies but often the companies have little control or access to data to enable the new provisions around such studies outlined in Article 101h to be adhered to.	
Page 7 Section 3.2.6	Provisions strengthening the role of EudraVigilance as a single, centralised pharmacovigilance database for the EEA are much needed and welcome. Limiting not only all third country reports, but also all domestic EU reports "*to go only into EudraVigilance*" is an excellent simplification initiative. However, the EC must takes steps to mandate the use of EudraVigilance and to ensure there is commitment from all Member States to adopt the requirement. Otherwise, complexity and costs will increase for all parties involved in the process.	This needs to be supported by rigorous enforcement of electronic reporting by MAHs to EMEA where Member states can access the reports, plus the transition of all competent authorities to ensure that their systems are ICH-E2B compliant and that all reports received by Member States are submitted to EMEA where Marketing Authorisation Holders must be able to access them.
Page 7 Section 3.2.6	We welcome that all serious 3rd country reports go to EudraVigilance only, noting that it is essential that individual competent authorities will commit to removing any local requirement to also submit directly to them as this would defeat the object of the proposal. With respect to the above, and to the second bullet which requires "*all EU domestic reports only to go to EudraVigilance*", it is a major change for all ICSRs to	Suggest that, all reports not being equal, timeframes for reporting continue to reflect the seriousness of the ICSR in question, as per current requirements.

	be required well within 15 days (regardless of seriousness and/or expectedness). If this is to be the case, it will present a huge logistical problem to industry in terms of prioritising workload, plus presumably Agencies will need to provide industry with both SAES and NSAES sent directly to them within the same timeframes.	
Page 7 Section 3.2.6	All case reports going to EudraVigilance should be in the English language, to save time and costs to regulators and industry. This would also improve the ability of both regulators and industry to analyse aggregate data.	The language used in all EU-sourced reports in Articles 101d and 101e should make it clear that reports are to be submitted to EudraVigilance in the English language. The proposed legislation should also specify:
Page 7 Section 3.2.6	Scanning the 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-EU compliance obligations can be met by multinational companies - all relevant cases should be made to relevant MAHs within 15 days so that foreign expedited reporting requirements can be met. Unless a rapid, robust and foolproof system is in place to achieve this, MAHs still will be obliged to continue literature screening themselves in order to meet the requirements of non-EU regulations. Some practicalities of this provision are not completely clear: Who will have responsibility for carrying out searches on local non-English language literature? Will the Agency use the same standards for literature	**Define** the scope of literature searches that will be performed by the EMEA and how the data will be made available to rapidly alert MAHs of any new ADRs arising from these searches. **Please clarify** whether the EMEA will use the same standards for literature review and follow up as currently detailed in Volume 9A for MAHs, and whether they will enter the same data into the database as ICSRs. **Please clarify** whether the MAH is still responsible for monitoring local medical literature or will this become the responsibility of the competent authority of the Member States?

	review as detailed in Volume 9A and will they enter the same data into the database as ICSRs? It is rare that a publication has all the information required to make a full assessment of the case. Will the Agency follow up on literature reports for more information? Will the EMEA send a note to the authors seeking additional information or will the EMEA ask the MAH to follow up with the author for more information? How will MAHs be informed or have access to reports from the scientific literature entered to EurdraVigilance in the context of literature scanning, to keep their own databases up to date?	
Page 7 Section 3.2.6	Articles relating to innovative products are of direct interest to MAHs during the peri-authorisation period in order to perform an adequate benefit-risk assessment. Furthermore, the innovative industry is the party that for many publications that definitively link literature cases with those reported earlier as clinical trial case reports. For newly approved products (since there are many publications), the proposal puts a significant burden on the EMEA, but does not reduce the burden for the industry and also increases the potential for duplicate reporting to EudraVigilance. Therefore, we recommend that the proposal for EMEA to scan and data enter case reports from the published literature is limited to mature, off-patent products.	**Amend to:** *"…the EMEA to take on new tasks, clearly defined in scope, for scanning of the scientific literature* ***for mature, off-patent products*** *and entering case reports from the literature on* ***EudraVigilance****, rather than the duplication currently conducted by the industry."*

	If there are problems with literature report duplications due to multiple companies submitting generic product reports, clarify regulation for companies to report to EMEA only on Trade Names Products and EMEA can scan for generics. The EMEA might like to pursue a global regulatory policy for literature reporting on generic drugs if regulators are being inundated with duplicate reports.	
Page 7 Section 3.2.6	'Side effect' reporting by patients raises some medical challenges which must be carefully considered and appropriately managed. The current legislative proposal does not indicate that mechanisms will be put in place to distinguish direct patient reports from medically confirmed report in the EMEA database. It is possible that this could lead to increased duplicate reporting to EudraVigilance if patients notify both the MAH and the national authority. In addition, Healthcare Professionals and patients should both have the choice to report to the MAH or to the member states websites. It is not acceptable to consider that the MAH is able to manage only the patients reporting for the intensively monitored drugs.	A **pilot** phase and subsequent careful evaluation of this proposal is warranted. **Please clarify** the purpose, mechanisms and scope of patient ADR reporting. **Please clarify** the safeguards to be put in place to identify and manage possible inappropriate reports.
Page 7 Section 3.2.6	Asking patients to report all suspected ADRs for medicines under intense monitoring will increase the number of consumer reports and raises a number of questions, namely:	

	• How does an MAH maintain the quality of spontaneous ADR reports amidst the increase in volume of reports which this change will generate? • For critical events how does the MAH ensure HCP confirmation of an ADR? • Does this imply any changes for the reportability of consumer reports directly reported to the MAH? • Will the EMEA web-page accept all reports in all languages? • Who will perform the translations? • What will be the transition process for reporting when a product comes 'off' intensive monitoring? Does this request impact PSURS for medicines under intensive monitoring?	
Page 7 Section 3.2.6	Patient adverse reaction reporting forms should <u>not</u> be part of the patient information leaflet. Given that the proposal has significant implications for manufacturing packaging costs, is there any evidence that such a system will 1- increase reporting from patients? 2- provide better quality data? 3- benefit the protection of public health? This requirement could lead to significant over-expediting of relatively low-value cases, particularly if the MAH is not given the legal means to use medical judgment in assessing the possible causality in the absence of a treating physician's attribution statement	Suggest that the ADR reporting form is distributed for products under intensive monitoring by pharmacists and physicians, separate from the packs containing these products. Alternatively, a web-based centralised reporting system will be more efficient as referred in comments on Article 101i, in addition to the current existing system established at the Member State level and via the MAH's PV system. **Amend to:** *'Make clear the legal basis for patients to report suspected adverse drug reactions:* ➢ ***<u>MAHs to provide toll-free company telephone numbers</u>***

	(see comments on Article 101e). Most likely patients would discard such forms at the time the package was opened; it is known that many patients do not read the patient information leaflet. The patient over time may have several possible ADRs to report but have only a limited number of forms if this is the preferred mechanism for the patient to report. Inserting an ADR reporting form into each pack will make current packs much bigger and necessitate significant change to companies' manufacturing capabilities, especially given the multiple language requirements within the EEA, presenting a significant issue from a resource/cost impact perspective for industry. The increased size of the patient information leaflet will make each package insert more bulky and potentially more difficult to get into the carton with the medication. It might be that packs would need to increase in size to accommodate this, with attendant transportation and storage costs for distributors and retailers. There is some concern that, by providing patients with ADR reporting forms in this way, HCPs would feel less obligated to report potentially significant SAEs since a reporting mechanism was being provided to consumers. Also, although some patients are knowledgeable and provide clear reports, it must be recognized that patient reports can be difficult to interpret when evaluating the drug. If such forms were to be introduced, would readability	***to collect adverse reaction reports from patients*** *~~Patient adverse reaction reporting forms to be part of the patient information leaflet for intensively monitored drugs, with reports going to the Marketing Authorisation holder,~~* ➢ *for ~~all other~~ **generic** drugs reporting via web-sites, directly to the national authority'*

	testing of the form need to be conducted at the same time as the patient information leaflet? We suggest that alternatives are considered: • Apply the requirement only for products under intensive monitoring • Distribute the ADR reporting form separately from the packs • Empower patients to report side effects via toll-free company telephone numbers and company owned/monitored websites. This would be a more efficient and effective way to collect the information as well as to collect any follow up information. It would also facilitate reporting from people who don't have ready access to web technology and would be less costly/time consuming for patient. For generic drugs, reporting could be achieved via web sites, directly to the national authority.	
Page 7 Section 3.2.6	The idea of placing a medicinal product on a list of intensely monitored medicines raises the following issues: 1. It could create a perception in the mind of the prescriber that medications not on the list are safe and thus don't require monitoring, ie, ADR reporting. 2. It could stimulate ADR reporting for those drugs on the list, thereby creating a disproportional safety profile for those on the list compared to	A detailed guideline with the purpose of intensive monitoring, standard criteria for inclusion onto this list, what the period of intensive monitoring will be; further guidance/clarity around how and when the list will be reviewed/maintained especially for timing of products to be removed from the list should be developed. **Please clarify** the criteria for inclusion on the list of products subject to intensive monitoring. **Clarify** the periodicity for reassessment of this requirement, and the criteria for removal of the requirement for intensive

	others in the same therapeutic class not on the list. 3. Reporting of adverse reactions on all other drugs directly to the national health authority limits the MAH's access to important safety information on their products and impedes their ability to perform risk assessment. Reporting routes for all products should be the same. 4. How will patients and health professionals will be alerted to this list apart from SmPC/PIL? Will it be a process similar to the UK Black Triangle? Companies with more proactive surveillance strategies may identify more safety signals on their products than their competitors in the same therapeutic class. If the number of safety issues is used as a criterion for inclusion on the list of intensely monitored products, it may place such companies at a competitive disadvantage. What are the criteria for inclusion into this list? It is unclear from the proposal whether the requirement for intensive surveillance will apply to all new medicines, or whether there will be a risk assessment done before authorisation that would allow some products to be left off the list of intensely monitored drugs. Would the list of intensively monitored products be those that have a formal Risk Management Plan in addition to the SPC and routine pharmacovigilance specification? Postings should include benefits of the product as well as the potential risk being monitored.	surveillance. Lists of products under intensive monitoring should be maintained at the EU rather than the MS level.

	It might be that all newly approved medicinal products could be included for a specified period of time. This time may be extended if safety issues arise. If older products are placed on this list, all products within the same therapeutic class should be included. It should be acknowledged that this could generate stimulated reporting. The provision could also result in biased over- or under- reporting of ADRs, depending on the audience and how it interprets the meaning of intensive surveillance. The criteria for removing medicinal products from the list should be specified. It is unclear when and how the requirement for intensive surveillance will be reassessed and subsequently removed when a safety profile has been established. In addition, 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 on Pharmacovigilance? It would also be helpful to have a clear target date for a first review of the status of a product. While observing proportionality between ADR reporting and the level of knowledge about the safety of a medicine is a sensible idea, a question has to be asked regarding products which are no longer deemed as medicines under intensive monitoring (because they are no longer new) but which are effectively under intensive monitoring because a safety signal is being	

	investigated. Would those products need to be reclassified as medicines under intensive monitoring and be relabelled, or would they simply be the subject of heightened vigilance by the MAH? It will be important to ensure that individual countries do not have their own lists of compounds under intensive monitoring, as is the case at present, in addition to that maintained at an EU level. The process by which the public list is established and maintained should be subjected to public consultation prior to implementation.	
Page 7 Section 3.2.6 & Article 101a	We have the following comments and concerns regarding the list of medicines under intensive monitoring: • 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 should not be underestimated and should therefore be carefully assessed.	**Please add** the following to the proposed Article 101j: ***'The Agency shall have due regard to the legitimate interest of marketing authorisation holders and other persons in the protection of their commercial interests and ensure that inclusion of products in and removal from such a list is managed in a transparent manner, and that all stakeholders concerned have been actively involved in concluding/finalising the details of such proposals.'***

	• 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). 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. It is therefore imperative that implementation of such a list is supported by appropriate measures/tools and educational activities across Member States to this end.	
Page 7 Section 3.2.6	Mention is made to report of medication errors that result in adverse reactions only. Medication error 'near misses' where the patient did not receive the product could also provide valuable information – especially with regard to cases of name confusion/packaging similarities. These should be reported also – as consistent with Volume 9A i.e. it should only be cases that are <u>not</u> associated with adverse reactions and near misses that should be reported in accordance with any additional national requirements. However, there should be a distinction made between medication errors resulting in a serious outcome (or 'near misses' that may have resulted in a serious outcome) and all other reports of medication errors. Only medication errors (or near misses) resulting in a serious outcome (or that could have resulted in a serious outcome) should be expeditable. A series of	**Amend to:** *"Regarding medication errors the definition of adverse drug reaction would be clarified as would the reporting rules to make clear that medication errors that result in an adverse reaction, **<u>and near misses</u>**, should be reported to the competent authorities for medicines (and oblige Member States to ensure any Patient Safety authority is also notified)."*

	scenarios should be defined in the updated version of Volume 9A to help clarify how to handle reports of medication errors. Will the definition of 'medication error' include all medication error scenarios such as maladministration, accidental exposure, dispensing errors, overdose etc ? Finally, it should be recognised that primary responsibility for recognising and reporting medication errors that result in adverse reactions lies with the healthcare delivery system and not with MAHs. MAHs would report medication errors of which they become aware, but an active surveillance system and 'policing' of medication errors within the community should not be an MAH responsibility.	
Page 8 Section 3.2.7	The text proposes no PSURs for old established products but in the associated changes in Article 101f, there is no derogation from the requirement to submit PSURs for innovator products that are old and established. The derogations quoted relate to applications submitted as generics, well established use etc.	Make the derogation for requiring PSURs independent from the legal basis of the registration application
Page 8 Section 3.2.7	The proposal to stratify the requirements on PSUR submission related to knowledge on the safety of the product and also formalization of the work-sharing projects to avoid duplication of work is supported. However, the MAHs should be closely involved in the planning of the proposed formalization of the work-sharing project.	**Amend to:** '*Where there is no risk management plan, provide for periodicity of reporting to be proportional to the knowledge of safety e.g.* **reduced periodicity of PSURs or** *no* **requirement for** *PSURs for old established products.'* **Please define** 'old established products'.

	It would seem unwise to abandon PSURs for all 'old' products, as new issues may arise with older products, resulting in variations to the marketing authorisation. For older products with reduced AE volumes, sometimes the only way to detect signals is through reviewing aggregate report data - PSURs support the principle of ongoing/long-term review of safety. 'Old' products may also be approved for new indications. Hence, it may be more appropriate for PSURs to be written for such 'old established products' at a reduced periodicity rather than abandoned altogether. Although the proposed change would reduce workload for companies and regulators, there would need to be consideration of matters such as when they need be to be re-initiated, a definition of what constitutes an "old product", the label change process in their absence, etc. Which body decides? Is this a condition that is to be requested by the MAH, or is it independently granted? Please note that companies would still have to prepare PSURs for some non-EU regulatory authorities.	Language regarding periodicity of reporting and proportionality to safety, including no PSURs for old established products, should be added to the proposed language under Title IX, Article 101f, 2 d). Consider introducing 'simplified' PSURs (e.g. an executive summary) for some older products that may still require regular overview of safety.
Page 8 Section 3.2.7	The concept of "linking" a PSUR to risk management planning has basic merit, but it is not possible to comment on it due to the complete absence of regulatory guidance on this topic. It has also to be considered that approval dates vary from one region to the other (US, EU). All products with an existing RMP require a PSUR according to the standard schedule. It is important to	Please clarify how "linking" would work. Recommend strengthening the proposal to the greatest extent possible to minimise the opportunity for Member States to impose reporting timeframes, intervals, and content that are not synchronised with the rest of the EU.

	define a harmonised single standard for the whole of Europe.	
Page 8 Section 3.2.7	Electronic reporting of PSURs has no defined standards or processes. Need to first define, test and implement standards for electronic reporting of PSURs before making it a regulatory requirement for MAHs.	
Page 8 Section 3.2.7	How will feedback on the quality of PSURs be provided to the MAH? What is the timeframe for PSUR assessment reports to be completed? (Must be less than 4 months in order to allow MAH to respond in next PSUR).	Clarify the working of the EU PSUR Assessment Group and specify the timelines for assessment reports to be completed and sent to the MAH.
Page 9 Section 3.2.8	It should be clarified that safety information made public via the EMEA portal or websites of the Member States should be accompanied by benefit information and an educational component to provide context. Proposed presentation of information and the process for maintaining such information should be subject to stakeholder consultation.	
Page 9 Section 3.2.8	It is important to develop standards for data elements and associated controlled vocabularies for a global drug dictionary, not merely a drug dictionary for the EU, consistent with ICH M5 standards. The scope of the specific data elements required for the exchange and analysis of pharmacovigilance information in this regard should be limited to marketed products - confidential and proprietary information regarding investigational medicinal products should be protected from public disclosure.	

Page 9 Section 3.2.8 And Article 101i	We welcome the increased coordination of provision of safety information, but are concerned that significant differences in content of information could still exist between member states as the text makes it clear that EMEA will coordinate but not replace Member State communication How will the EMEA ensure consistent standards across 27 MS websites?	Suggest adding that there is one single contact point identified for the MAH for each product to report any safety issues. This could either be the EMEA, the Rapporteur or RMS or assigned PhVWP representative. The notification of the Regulator's Network would then be made along the same communication lines as for all other safety alerts.
Page 9 3.2.9 Clearer safety warnings in product information to improve the safe use of medicines	The rationale provided to justify the proposed introduction of a new section in the Summary of Product Characteristics and Patient Information Leaflet on key safety information is *'the current organisation of product information makes it difficult to identify the most important safety warnings'* which therefore '*may be missed'* The inclusion of new sections in the SmPC, highlighting key safety information, needs to be given careful consideration. We believe that the Summary of Product Characteristics and Patient Information Leaflet should be revised rather than added to, so that safety information is presented in a clear and understandable manner. Adding a new 'key safety information' section to the Summary of Product Characteristics and Patient Information Leaflet could be redundant with safety information provided elsewhere in these documents (e.g. Warnings and Precautions) and thus could cause confusion.	In the absence of any information on what the content of the new key safety section would be it is difficult to judge if this section would provide added value or if another existing section could be revised to meet the needs. Our first recommendation is that the Summary of Product Characteristics and Patient Information Leaflet should be revised rather than added to, so that safety information is presented in a clear and understandable manner.

	While such a section may be beneficial with respect to the prevention or management of safety issues included in that section, it may lead to less attention being paid to other important (but not "key"?) safety information elsewhere in the SmPC. Key safety information" and the manner in which it is presented must be clearly defined. The trigger for 'key' or 'most important' may vary with different products, the indications for use, severity of disease, or prognosis. In addition, what is important to one patient may be less important to another: Highlighting certain safety information may be disadvantageous as it may have the effect of de-emphasizing other essential information, for example, that other patients need. It could also have the effect of 'steering' certain patients toward or away from alternative therapies. It would be important to test the effectiveness of any new safety section to see if does not negatively impact the prescriber's and patient's understanding of the safety information. The required patient readability testing of patient information leaflets already documents the effectiveness of communicating important safety information to patients. Safety information should not appear before information on the indication. If this new section is retained in the legislation, guidance should be provided on how this section should be written (i.e., level of language) and define what comprises key safety information. It would also	

	be helpful to give some flexibility in relation to the timing for submitting such product information updates during the 5- year transitional phase and not necessarily link this to a renewal or a major variation. It is also important to communicate the benefits of a product and, in some cases, the risks of not taking the product.	

SECTION 4 – DETAILED PROPOSALS TO CHANGE EU LEGAL TEXTS		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
	No comments received.	

ANNEX 1 STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE/ DETAILED PROPOSALS FOR LEGISLATIVE CHANGES		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 11 Article 1(11)	The new definition of an 'adverse reaction' should be aligned with the harmonised definition recommended by ICH E2D guideline, as previously adopted by the CHMP (CHMP/ICH/3945/03). In particular, the definition should distinguish between the concepts of 'reaction' and 'event', especially as this definition	**Reinstate:** *'Adverse reaction: A response to a medicinal product which is noxious and unintended,* ***and which occurs at any dose used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. The phrase 'response to a medicinal product' means that a***

	covers AEs/ADRs solicited from post-authorisation studies, which require specific causality assessment, as well as those received as spontaneous reports. In addition, it should clarify that it applies to any dose used in clinical practice, so that it is clear that this definition is not restricted to the doses specified within the product's SPC.	***causal relationship is at least a reasonable possibility.'***
Page 11 Article 1(13)	The definition of 'unexpected ADR' has been removed, presumably because it is proposed that all serious ADRs will be subject to expedited notification, whether 'expected' or 'unexpected'. However, there is reference to 'unexpected' ADRs within the proposed Article 101a and, therefore, a definition is necessary. In addition, although this may not affect expedited reporting of individual case reports for a marketed product by the MAH in accordance with the new proposals, the concept of 'expectedness' is important when detecting new risks not covered in the SPC. The previous Article 1(13) should be re-instated.	**Re-instate**: '***Unexpected adverse reaction: An adverse reaction, the nature, severity of outcomes of which is not consistent with the summary of product characteristics.'***
Page 11 Article 1(13)	Article 101f indicates that (line) listings of individual cases will not be routinely required as part of PSUR submissions. However, by inference, it may be that line listings will be required in some circumstances, possibly with selected cases from some sources (as at present). If so, there could be a need to provide 'unlisted' ADR case reports as part of the line listings and, therefore, a definition of 'unlisted' ADRs should	**Add:** ***'Unlisted adverse reaction: An adverse reaction that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as***

	be added to Directive 2001/83/EC, as currently provided within Volume 9A.	***occurring with this product.'***
Page 11 Article 1 (16)	It is proposed to delete the definition of 'abuse of medicinal products'. However, it is important to differentiate between adverse events resulting from wilful abuse of authorised medicines compared with medication errors. Furthermore, this definition is relevant in the application of Article 71 of the Directive, in the determination of the appropriate prescription classification of medicinal products. We propose that the definition be retained, if not amended as proposed opposite. In addition, given that there are several references to medication errors within the proposed legislation, the term 'medication error' should be defined.	**Add:** ***'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.*** ***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.'***
Page 12 Article 1(15)	The proposed revision to the definition of a PASS is too broad and still contains some ambiguity which requires resolution. The current ambiguity has led to a variety of interpretations of the definition by MAHs resulting in outcomes ranging from inadequate company oversight of PASS, or non-inclusion of relevant studies in RMPs/PSURs, to inclusion of every post-marketing study and generation and reporting of data irrelevant to safety. MAHs are likely to be conservative, resulting in significant additional and often unnecessary work for	**Amend to:** "*Post-authorisation safety study: A pharmacoepidemiological study or a clinical trial with an authorised medicinal product,* ***carried out in accordance with the terms of the marketing authorisation with the stated objective*** *of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product.* ***This includes all such studies conducted within the EEA together with those conducted outside the EEA that form part of an EU Risk Management Plan."***

	both the MAH and the Competent Authorities. Replacement of the phrase "…*in accordance with the terms of the marketing authorisation*…" by "…*with an authorised medicinal product*…" broadens the scope too much such that it could now encompass any study conducted post-authorisation, including clinical trials designed to investigate the safety and efficacy of new formulations or indications for a product that is on the market (i.e. new clinical development activities, ordinarily covered by Directive 2001/20/EC). This would create overlap and conflicting and/or multiple duplicative requirements, and conflicts with the notion that the definition applies to studies that relate to the authorised use of a product, clearly what is not intended by this proposed change. If the intention is to cover off-label use with a medicinal product, then this can be covered by the definition as proposed opposite, with suitable explanatory text within Volume 9A. Furthermore, the definition should be consistent with the current definition of a 'non-interventional trial' in the Directive 2001/20/EC: *Non-interventional trial: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in*	

	the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data. An unambiguous definition is required, with a direct link to the authorised use of the product, as suggested in the next column. In addition, it should clarify the scope of the requirements in relation to relevant studies conducted outside of the EEA (see comment on Article 101h – page 26).	
Page 12 Article 1(33)	The use of the word 'system' for both the company general pharmacovigilance activities ('pharmacovigilance system') as well as the specific activities for a product ('risk management system') can lead to confusion. The proposed definition relates more to 'risk management activities' rather than a 'system'. Please note that the terms 'system' and 'plan' are used inconsistently throughout the proposed legislation - it is important to distinguish between the two and to ensure the correct term is used to avoid confusion. The proposed definition of a 'risk management system' should be clarified further with use of 'and/or', as suggested.	*'Risk management **activities**: a set of pharmacovigilance activities and/or interventions designed to identify, characterise, prevent **and**/or minimise risks relating to a specific medicinal product, including the assessment of the effectiveness of those interventions.'*
Page 12 Article 8(3)(ia)	The obligation for the QPPV to sign a statement saying that the applicant has the means to fulfil the tasks and responsibilities listed in Title IX should not place personal liability on the QPPV as an individual, but should be a statement from the applicant company. The	**Amend to:** *"…a statement signed by the **applicant company** to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX…"*

	QPPV should not be held accountable to a standard or requirement that is not and cannot be clearly defined.	
Page 12 Article 8 (3)(iaa),	In Section 3.2.4 "Impact", it is specified that Risk Management Plans are only to be submitted when they are needed. This should be recognized in this article.	Amend to: '**<u>If *applicable*</u>** *a detailed description of the risk management system….'*
Page 13 Article 8(3)(iaa)	With regards to the statement "…*risk management system shall be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product*.": Which body assesses the adequacy of proportionality? What measures will be adopted to guarantee an adequate level of consistency across evaluators within the competent authorities?	**Please clarify.**
Directive 2001/83/EC Art.11(3b) Page 13 *'key safety information about the medicinal product and how to minimise risk'*	It is not relevant to include all the risk minimisation activities included in the product's risk management plan in the 'key safety information of the SmPC, such as restrictions in distribution, reminders for lab tests. Considering that these activities may change over time, it is important to clarify which types of risk minimisation activities should be detailed in the SmPC and/or package leaflet, primarily those aimed at influencing clinical practice. This information should not duplicate that already presented within 'Warnings & Precautions'.	
Directive 2001/83/EC, Article 11 (3b) 2nd and 3rd sentence	The inclusion of new sections in the SmPC, highlighting key safety information, needs to be given careful consideration. While this may be beneficial with respect to the prevention or management of safety	*3b ~~key safety information about the medicinal product and how to minimise risks.~~ For medicinal products included on the European list of intensively monitored products referred to in Article 101j ~~this information shall also~~ include the*

'*For medicinal products included on the European list of intensively monitored products referred to in Article 101j this information shall also include the statement "This medicinal product is under intensive monitoring. All suspected adverse reaction should be reported"'* *Page 13*	issues included in that section, it may lead to less attention being paid to other important (but not "key"?) safety information elsewhere in the SmPC. "Key safety information" and the manner in which it is presented must be clearly defined. The information should be limited to the most important safety information, critical to the appropriate use of the product, and should reference, rather than repeat, more detailed information elsewhere in the SmPC and therefore there will need to be guidance on what is meant by "key safety information". Furthermore the risk of imposing too much focus on risks is high and this may result in the product never being used according to its potential benefits and its clinical safety never being fully documented because of reputation is bad for lifecycle. It is also essential that this provision is applied consistently, across different medicinal products and by all European competent authorities, so as not to give a false impression of the relative safety of products. There is concern that the provision may discredit a large number of new products potentially being more effective and safer than existing alternatives and therefore the retrospective application of this provision to already authorised products must also be considered, so as not to give the impression that newer products are in some way less safe than older ones There is a need for clear guidance addressing all of these points.	*statement "This medicinal product* ~~*is under intensive monitoring*~~ ***has recently been approved for use in [indication]. "***

	See also comment on Article 59.	
Page 14 Article 21(1)	If the description of the Risk Management System is to be annexed to the Marketing Authorisation (MA), due to the frequent changes in this system, the procedure to introduce a variation should not be a type II variation. The RMP is a large detailed document with potential proprietary information. Providing all the details of the agreed risk management system may not be compatible with the principles of deletion of commercially confidential information. It should not be necessary to add the entire document to the MA – we suggest that only a summary of the risk management plan be annexed to the MA. This summary should be specially written to be understandable by patients and members of the general public in order to comply with the provision of better information about medicines. Please note that the terms 's*ystem'* and '*plan'* are used interchangeably throughout proposed legislation (e.g. Article 101i Chapter 5 page 28 states risk management *plan*). Ensure consistency – if there is an intended distinction between the terms it should be clarified.	Risk Management System changes should be subject to Type IA notification. **Amend to:** ***"A summary** of the risk management system shall be annexed to the marketing authorisation."* **Please clarify** if there is any distinction between the terms 'system' and 'plan', or ensure that they are used consistently throughout the legislation.
Page 14 Article 21 bullet 3	Clarification is needed concerning what part of the Marketing Authorisation will be made public. We have concern over proprietary information being released and also over privacy concerns if the names of a MAH's employees are made public.	**Please clarify** which components of the MA are to be made public.
Page 14	The proposed text provides that the competent	**Amend to:**

Article 21 (4)	authorities shall draw up an assessment report as regards the risk management system. As the possible risks with a product should be the same regardless of where the product is marketed the text should emphasise that there should be one single global risk management plan for each NCE. Transposition of RMP actions into national mitigation activities can then be used to cover differences in local medical practice and/or specific national legislated requirements.	*"….and as regards the risk management system of the medicinal product concerned.* ***The risk management plan for the product concerned should, unless there is a strong justification, be the same regardless of where the product is marketed****. The assessment report…"*
Pages 14-16 Directive 2001/83/EC Article 22 (1) Regulation (EC) No 726/2004, Article 9(4)(c), 14 (8)	The introduction of a clearer legal basis for post approval commitments should not be through removal of the option for an authorisation under exceptional circumstances. The current provisions on marketing authorisation under exceptional circumstances make reference to grounds set out in Annex I of the Directive (i.e. inability to provide comprehensive efficacy or safety data because of rarity of the disease, present scientific knowledge or ethical principles). As the current provisions have been applied in the case of important new drugs (e.g. for treatment of HIV and sepsis), we believe that they should be retained. The text for post-authorisation commitments should be an addition to the current article.	Current text of Article 22 [and Article 14 (8) of Regulation (EC) No 726/2004] to be retained. Proposed text for Article 22 to be included as Article 22a
Page 15 Directive 2001/83/EC Article 22 (1) Regulation (EC) No 726/2004, Article 9(4)(c),	Deadlines for the fulfilment of certain conditions where necessary should be realistic and MAHs should be consulted.	Modification of some of the proposed text of what would be Article 22a (1) is proposed below: "1. *A marketing authorisation may be granted* a) *the requirement to conduct post-authorisation safety studies* **and**/*or* b) *adverse reactions recording or reporting that differs from*

14 (8)		*the requirements of Title IX* **and**/*or* c) *any conditions….* *The marketing authorisation shall lay down deadlines in consultation with the MAH/applicant for the fulfilment of the conditions where necessary. Continuation of the authorisation ~~shall~~ may be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions.'* Please provide definitions or criteria to clarify how it will be determined whether deadlines are necessary and how these deadlines will be set. In particular how will feasibility be taken into account?
Pages 15-16 Directive 2001/83/EC Article 22 (2)	There is insufficient explanation as to how the "list of intensively monitored products" will be developed and implemented. Such a list should not be implemented until there is a clear understanding of the impact that it would have on the relative perception of products and, ultimately, patients' access to those products. This type of list could run a high risk of branding certain products as inferior even though that is not the intent. Furthermore, the conditions listed in the first paragraph do not necessarily translate an identified need for intensive monitoring. For example, a PASS may be required to better understand the mechanism of action of a certain adverse reaction, but it doesn't mean that patients and physicians should be reporting all ADRs for this	Please **amend** to: ".2. *The Member States shall notify to the Agency the granting of marketing authorisations subject to conditions as referred to in paragraph 1 and these medicinal products shall be included, **if appropriate**, in the European list of intensively monitored products referred to in Article 101j.* "***The Agency will remove*** *a ~~A~~ medicinal product ~~shall be removed~~ from the list when …"*

	product in an intensive manner.	
Page 16 Directive 2001/83/EC Article 23 4th paragraph, 1st sentence Regulation (EC) No 726/2004 Article 16 (2), 2nd paragraph	The 4th paragraph of Article 23 clarifies that the new information which may influence the benefit and risk of the medicinal product for human use includes *'results of clinical trials'* Marketing authorisation holders may not have been made aware of all investigator- initiated clinical trials undertaken with their products. This needs to be taken into consideration. It would be helpful that a supportive guidance text be developed in relation to the implementation of the provisions set out in this paragraph (current and new provisions)	Please **amend** to: "*In particular he shall forthwith inform the competent authority …of any new information, including results of clinical trials* ***sponsored by the marketing authorisation holder,*** *which might influence…"*
Page 16 Directive 2001/83/EC Article 23 4th paragraph, 2nd sentence Regulation (EC) No 726/2004 Article 16 (2), 2nd paragraph	*'He shall ensure that the product information is kept up to date with the current scientific knowledge including assessment conclusions made public via the European medicines safety web-portal referred to in Article 101i'* The breadth of the requirement for the MAH to keep product information up to date needs to be clarified in order that sensible labelling practices can prevail An appropriate process will be needed to ensure that the product information and the information on the European medicines safety web-portal are consistent.	
Page 17 Regulation 726/2004	With regards to the statement "*The competent authority may at any time ask the holder of the marketing authorisation to submit a copy of the*	Please c**larify** the timeframe for submission upon request.

Article 16	*pharmacovigilance system master file*", please clarify the expected timeframe for submission by the MAH.	
Page 19 Directive 2001/83/EC Article 54 (o)	The addition of text to indicate that the product is under intensive monitoring to the outer packaging is not supported. This message is aimed primarily at the healthcare professional and should therefore be conveyed through the SmPC. Furthermore this could be interpreted as suggesting that ARs should not be reported for the other products. Patients also may not understand the difference between "suspected" and other ARs. Furthermore, finding space on the packs would be a major issue, especially when the packs are multi-lingual or small; potential impact might be to have to create bigger cartons, which has significant technical and cost implications. Companies are already finding it challenging to find suitable space for Braille, serialisation, paediatric logo, etc.). If text is added over the Braille on packs (because there is no other space for it), it may obscure the print legibility. In view of the above, if after discussion with all stakeholders it is considered necessary to have something on the outer packaging a pictogram or symbol would be more acceptable but with caution based on experience of the paediatric logo (takes a long time, consensus difficult, cultural interpretation seems more challenging with pictures than with words).	Please **delete** *(o)*
Pages 19-20 Directive 2001/83/EC	We question the benefit of the inclusion of "black box" text in the PIL, as it may distract patients from other important information, and may also raise unnecessary	Please **delete**. ~~*Key safety information about the medicinal products and how to minimise risks. This information shall be presented in a box surrounded by a black border'*~~

Article 59 (ba) First and second sentence *'Key safety information about the medicinal products and how to minimise risks. This information shall be presented in a box surrounded by a black border'*	concerns, potentially leading to reduced compliance and increased risks to patients. Furthermore a box with black borders could be confusing as compared with black box warnings in US labels. Patients should be encouraged to read the complete PIL, not just a small section, albeit of "key" information. It would be more appropriate to highlight key information (e.g. using emboldening or colours) in the relevant sections and to place more emphasis on those aspects which are conducive of risk minimisation rather than on the risks themselves. The revisions to 2001/83 in 2005 to reorder the information and introduce readability testing aim to achieve clear information for patients. Until these changes have been fully implemented and their effectiveness evaluated, it would be inappropriate to introduce another change in format. This could be considered in the future if current changes being implemented are not found to have been effective in improving information to patients. We respectfully suggest that in this event the European Commission consult with user testing experts to ensure that an appropriate layout and template is utilised for presentation of the information.	
Pages 19 Directive 2001/83/EC Article 59 (ba) 3rd and 4th sentences *'For medicinal products*	The addition of text to indicate that the product is under intensive monitoring is not supported. This message is aimed primarily at the healthcare professional and should therefore be conveyed through the SmPC and /or on the safety website An additional caveat would be that this statement being	Please, **delete.**

included on the European list of intensively monitored products referred to in Article 101j the following additional statement shall be included" This medicinal porudtc is under intensive mornitoring'	in the PIL would make it necessary to change the PIL whenever the product is placed on or removed from the list referred to in Article 101j . If nevertheless a statement was to be introduced we would believe that the currently proposed statement is inappropriate to ensure necessary confidence in the new product and support compliance. The template of the package leaflet already provides *'if any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor> <or> <pharmacist>* We believe adding a different or further statement may create confusion.	If an additional statement was to be included, the following wording would be more appropriate to support compliance: (c)' *For medicinal products….* *This medicinal product* ***has in assessment by the regulatory authorities demonstrated that it fulfils the necessary standards required for the granting of a marketing authorisation. As additional information about <product name> use in the wider patient population will further improve the knowledge of its optimal use, <product name>*** *is under 'intensive' monitoring.*~~"~~
Pages 19 Directive 2001/83/EC Article 59 (ba) 5th (last) sentence.	Sometimes the MAH is the mother company, while local reactions are being collected by the affiliate, which is not the MAH, so it should be possible for patients to report ADRs to the local company even if it is not the MAH. It must also be noted that if patient AE forms are attached to the PIL (an option that we do not support for the reasons listed in our general comments) or on CA web sites then they should include a requirement for the patient to consent to the use/disclosure of such information as a condition to submission of the AE. The consent should be such that it is effective under EU Data Privacy laws and permits reporting, follow-up with HCPs and sharing information across regions as is necessary for management of AEs.	If the proposal to include a specific wording on the need to report side effect was maintained it is suggested to modify it as follows: *"All suspected adverse reactions should be reported to < the name and address of the marketing authorisation holder or* ***if applicable its local representative*** *in the Member State where the marketing authorisation holder will receive suspected adverse reaction reports >"*

Directive 2001/83/EC Title IX (Article 101-108) 'Pharmacovigilance'		
CHAPTER 1		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 20 Article 101a	The first two paragraphs are not directly linked to the heading and have a broader scope; they should be above the title or have their own article.	**Please amend** accordingly.
Page 20 Article 101a	The term 'doctor' has been used and it is suggested that it should be replaced with 'physician' in order to remove possible ambiguity. In addition, the requirement on Member States to actively encourage healthcare professionals to report suspected ADRs could be restricted to medicines under intensive monitoring, and perhaps any other medicines where reporting is encouraged by the black box warning. Please note that healthcare professionals and patients are more likely to report ADRs if they understand the impact the reports can have (positive or negative) on a safety profile. We suggest that an advertising campaign for patients, to highlight the importance of reporting and give examples from the past when ADR reports have changed the safety profile of a product, would be valuable.	**Amend to:** The Member States shall take all appropriate measures to encourage ~~doctors~~ physicians and other health care professionals to report suspected adverse reactions to the marketing authorisation holder or the competent authorities, especially with regards to medicines under intensive monitoring referred to in Article 101j."
Page 20	EFPIA supports the need to ensure that biological medicinal products are clearly identifiable. We	We suggest to **deleting** the proposed third part of Article 101a and replace it by an obligation for the newly created

Article 101a	nevertheless regret that the Commission has not made any specific proposal on how to ensure proper and clear identification of such products when prescribed and dispensed within the EEA, 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 levels, and 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 biological substances with the same International Non-Proprietary Name (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. Therefore,	committee 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.

	for effective pharmacovigilance of biologicals, it is essential that each suspected 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 uniform approach for ensuring clear and proper identification of biological medicinal products in Europe. There is a need for urgent regulatory action in this respect since so-called 'biosimilar' medicines have already been approved by the Commission, including biosimilar medicines that bear the same INN as the innovator reference product. The above proposal fits in 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 CHMP. This committee could be entrusted with the responsibility of making prompt proposals for the clear and proper identification of <u>all</u> 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.	
Page 20 Article 101a	Under current legislation, it is difficult to see how a Member State can ensure that an ADR associated with a biological product is identifiable where biosimilar	**Revise** the legislation to require that: • a distinct INN be assigned to each biosimilar

	products are available in that country. It is important that "*identifiable*" should be specified in such a way that it will always lead to the right product and this should be addressed specifically within the revised legislation. Without legally supported mandatory detail in nomenclature of biologics, it is difficult to see how it could be possible to link the incidence of events with a particular source or presentation of a biological medicinal product. It is critical to be able to uniquely identify and trace a biological medicinal product for two reasons: 1) to avoid confounding the post-marketing surveillance and risk management activities required in order to identify any rare immunological side effects, *2)* to be able to quickly identify a specific biological product associated with any quality issues or adverse events. To enable identification, distinct and unique INNs for biosimilars should be adopted and this should be mandated in the legislation. The allocation of a unique INN for each biological product would enable MAHs to link rare but serious side effects with the correct product, responsibly monitor and manage safety issues associated with their product and minimize risk to patients. This is particularly true in jurisdictions where generic or therapeutic substitution occurs, or where no record is made of the product actually dispensed or administered to patients.	medicinal product from a different manufacturer, and • it is not permissible to substitute with a biosimilar medicinal product without the prescribing physician's agreement

	A unique INN would also facilitate effective communication and exchange of information among health professionals. Conversely, giving a biosimilar product the same INN as the innovative product will make tracing ADRs more difficult and may give the false impression that the products are the same and therefore substitutable. We would therefore strongly recommend that the legislation requires that: • A distinct INN be assigned to each biosimilar medicinal product from a different manufacturer • It is not permissible to substitute with a biosimilar product without the prescribing physician's agreement.	
Page 20 Article 101a para 3	Non-prescribed/dispensed medicines should also be subject to adverse reaction reporting.	Please **amend to:** *'…any biological medicinal product prescribed, dispensed **or sold** in their territory which is the subject of an adverse reaction report…'*

CHAPTER 2		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 20 Article 101(b)	The introduction of GVP is supported, however the detail of sections to be covered should be removed from the legislation to avoid unnecessary restrictions	Please **amend to:** "*Following consultation with the Agency, Member States,*

	when writing the supportive guidance. The supportive guidance should then be very specific so as to minimise variation in interpretation across Member States. Furthermore, the current proposal indicates that 'Good Vigilance Practice' would be written as a guideline. However, under section 3.2.2 (page 4), it indicates that the Commission wishes to adopt a regulation for 'Good Vigilance Practice' via comitology. We suggest that GVP should be covered by a regulation to ensure legal certainty and facilitate consistent public health protection. However, it is important that such a regulation replaces current directives and guidance, rather than adding to them, so as not to overburden both industry and competent authorities with additional requirements. We note that the proposed description has much overlap with requirements for pharmacovigilance that are already well defined. This area is already highly regulated through compliance obligations, so without greater specificity in the language, it is difficult to see at present how a 'GVP regulation' would add value rather than just adding to the burden, and how patients would be better protected (more than through existing regulations, directives and guidance). The 'interested parties' included in consultation process should include Marketing Authorisation Holders.	***Marketing Authorisation Holders and other*** *interested parties, and in accordance with the procedure referred to in Article 121 (2), the Commission may adopt ~~guidelines~~* ***a regulation*** *on good pharmacovigilance practice including technical rules and procedures*. ~~for:.~~ ~~the use of internationally agreed terminologies, including medical terminologies, for mats and standards for the conduct of pharmacovigilance.~~ ~~the electronic reporting of adverse reactions and the submission of reports to Eudravigilance in accordance with Article10 1e~~ ~~the monitoring by the Agency of the data in Eudravigilance for signals of new or changing risks in accordance with 101d.~~ ~~the format of periodic safety update reports submitted in accordance with Article 101f.~~ ~~the format of protocols and final study reports for the post - authorisation safety studies referred to in Art 101h.~~ ~~Procedures and formats for drug safety communications including the procedures for management of urgent communications in accordance with Article 101i.~~ ~~the operation of Article 101k.~~ ~~Scientific and procedural guidelines on audit by the Marketing Authorisation Holders, National Competent Authorities and Agency of their performance of pharmacovigilance .~~ *These guidelines shall be revised as necessary to take account of technical and scientific progress".*

CHAPTER 3		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
	No comments received.	

CHAPTER 4		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 22 Article 101d.2	Although it might be appropriate to delegate responsibility for monitoring the data in EudraVigilance to the EMEA, it is suggested that responsibility is divided according to the route of registration of the product to the Rapporteur, Reference Member State and national authorities, as appropriate. Roles and responsibilities of the Agency and the competent authorities in signal detection should be specified - common and consistent methodology for monitoring the data in EudraVigilance should be adopted and shared. Steps between identification of a signal and confirmation of a change are not included in the text. What would be expected to happen upon identification of a signal? Would the MAH be involved in its evaluation?	Please **amend to:** ***"2. In accordance with the procedure referred to in Article 121 (2) the Commission may adopt guidelines on the 'Roles and responsibilities of the Agency and the competent authorities in signal detection',*** *the Agency, in collaboration with the Member State Competent Authorities, shall monitor the data in EudraVigilance for signals of new or changing risks of medicinal products authorised in the Community. In the event of a change being detected the Agency shall inform all marketing authorisation holders, the Member States and the Commission of these findings.* ***The Rapporteur, Reference Member State and***

	Finally, MAHs should be able to access data for their products from Eudravigilance.	***national competent authorities will remain the supervising authority for pharmacovigilance, as appropriate.*** *Wording should be added to clarify the continuum between generation of a safety signal and the steps taken to confirm or refute it. The MAH, in consultation with the competent authorities, should be involved in evaluating the potential signal."*
Page 22 Article 101d.3	We suggest that this provision should be deleted. The objective to make individual adverse reaction reports held on EudraVigilance publicly available upon request currently appears to be unclear. Clarity is requested regarding the rationale, practicality and benefit of providing this information. 'Individual adverse reaction reports' is not the usual term to designate 'Individual Case Safety Reports' (ICSRs) that are held on the EudraVigilance database – ICSRs should be used in this context within such proposed legislation. Even though it is stated that the anonymity of patients will be maintained, we have great concern about allowing public access to what amounts to 'raw data'. The provision of access to EudraVigilance data needs to take into account the often incomplete nature of post-marketing safety reports, which necessitates informed interpretation of such data and full appreciation of its limitations. In addition to overlooking the role and responsibility of national competent authorities in acting as the interface between EudraVigilance, patients and healthcare professionals, provision of full direct public access to individual case safety	**Please delete this provision -** consideration should be given to alternative approaches to making safety data available to the public in a meaningful manner. **If the sentence can not be deleted, amend to:** *"3. Individual ~~adverse reaction~~* ***case safety*** *reports held on the EudraVigilance database may be requested by the public ~~and these data~~.* ***In response, relevant information*** *shall be provided by the Agency or the national competent authority from whom they were requested within 90 days ~~unless this would~~* ***in a manner that does not*** *compromise the anonymity of ~~the subjects of~~* ***any individual mentioned in the report, and so that the data can be readily and accurately interpreted by the public, including its limitations and constraints."***

	report (ICSR) data could carry significant risks to public health within the European Union: • There could be a significant danger of over-interpretation of such data by persons lacking the necessary skills, medical as well as statistical and epidemiological, to interpret and understand it, with a potential for generating unnecessary health scares; • There could be a significant risk that patients will abreact and simply stop their own medications unnecessarily in response to the receipt of such data (without consulting their healthcare providers first). Therefore, we propose that the public should request information in writing from their respective national authority, using their own national language. This would allow national authorities to respond in a manner that takes into account national cultural, medical and legal sensitivities. We also propose that Member State authorities should provide information from EudraVigilance in response to such requests in a consistent manner. Relevant pan-European information should be provided in the form of a table, similar to that currently provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) as 'Drug Analysis Prints' in response to such requests, accompanied by a summary evaluation of the data prepared by the authority, including an explanation of how the data relates to local medical practice and the national Summary of Product Characteristics for the product. These should be provided together with a disclaimer with regards to how the data may be interpreted by the patient and subsequently used, in a manner	

	that a patient would readily understand e.g. a conclusion on the benefit/risk balance and a recommendation to discuss the information sent with a health care professional. Applicable laws on the protection of individuals with regard to the processing of personal data and on the free movement of such data may need to be re-considered and discussion on the potential consequences of this should be re-evaluated. Not only should the anonymity of the subject(s) of the report be protected, but also of any subject mentioned in the report (e.g. reporter). Indeed, it may be possible that in some member states, national implementation of this paragraph will be impossible without a specific agreement of the patient concerned in order to avoid contravening data privacy regulations. Otherwise, if the proposal is to proceed as presented, the granting of public access to ICSRs 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). The Agency and national competent authorities should make clear in the relevant and appropriate implementing guidelines the type of information from ICSRs within EudraVigilance that may be provided upon request to the public. Further, the information provided by either the Agency or the national competent authorities should be standardised, taking into account applicable privacy laws and patient confidentiality, as well as giving consideration to the well documented limitations of data collected via spontaneous reporting and potential misinterpretations being made from this data - the release of	

	data should be accompanied by clear disclaimers that put the data into the appropriate medical context. Finally, if the information provided relates to a specific product, the MAH should be informed that such information has been requested and provided.	
Page 22 Article 101d.3	If the public is allowed to request individual reports, the Agency or the national CA might be blocked by a lot of requests from just a few individuals (this has been seen in Germany with PEI). As a result, authorities may choose to provide unrestricted access, but this would compromise the anonymity of patients and reporters. Thus, authorities would need to re-code countless reports (new reports might be sent in a way where the identity is only visible to authority staff, but old reports would require additional work). Isolated individual reports only show a based situation of the safety of a medicinal product. PSUR assessment reports on the other hand show an overview of the safety profile of the medicinal product and would be much more appropriate as information for the public. It would be necessary though to provide information in all national EU languages because not everybody understands English sufficiently. The Agency would be responsible for translating the PSUR assessment reports.	**Alternative to the above suggestion:** '3. *PSUR assessment reports held on the EudraVigilance database may be requested by the public and these data shall be provided by the Agency or the national competent authority from whom they were requested within 90 days* **in a manner that allows the report to be readily and accurately interpreted by the public, including its limitations and constraints**.'
Page 22 Article 101e.1	Please clarify that these requirements only apply to spontaneous reports (and not reports from solicited sources). Assuming that this is the intention, by their very nature, spontaneous reports are only suspected adverse reactions until further evidence is brought to confirm the causal relationship. This article appears to elaborate the definition of an ADR	**Amend to:** *'Marketing authorisation holders shall record all* ***suspected*** *adverse reactions in the Community or in third countries which are brought to their attention* ***as spontaneous reports.*** *Adverse reactions recorded shall be reports where the Marketing Authorisation Holder*

	provided by Article 1(11). However, as proposed, it could encompass virtually all reports from post-marketing sources (including interventional and non-interventional studies, and registries) that lack a specific causality assessment by the reporting physician (or patient) i.e. it lacks any opportunity for the MAH to distinguish between (unrelated) adverse events and (suspected) adverse reactions in this situation. 1(a) requires the submission of adverse reactions for reports where the patient or the health care professional has made a statement of possible attribution. This will create a new EU requirement to submit non-HCP cases. Is the intent to rely on consumer causality as part of the ADR reporting paradigm? This has significant implications for the number and quality of reports in EudraVigilance. It also remains unclear whether all such reports must also be reported. If yes, this would mean that any patient's causality assessment is deemed as valid and as scientifically sound as a healthcare professional's assessment. How can a MAH consider that there is "*at least a reasonable possibility*" for a patient report, if there is no possibility at all to verify the report medically? This is even more difficult for reports from patients with mental illness, where it is absolutely vital to obtain a HCP confirmation. 1(b) requires the submission of all reports where no causality statement is made or the causality is unknown. This has significant implications, particularly if it is intended to include adverse events from non-interventional studies, for which it can be uncommon to receive a causality statement from the treating physician. MAHs are often required to conduct epidemiology studies, product usage surveys and other	*considers that a causal relationship is at least a reasonable possibility, and this shall include:* *(a)* ***All reports*** *where* ***the Healthcare Professional*** *has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; and* *(b)* ***Spontaneous*** *reports* ***arising from marketed use of the product*** *where the Patient or the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown but the temporal relationship between the exposure to the medicinal product and the adverse* ***event*** *means that a causal relationship* ***cannot*** *be excluded.* ***(c) Reports of serious adverse events arising from post-authorisation studies where the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown but the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility.*** ***Reports from patients shall be recorded but need confirmation from a Healthcare Professional in order to qualify as suspected adverse reactions.'*** **Please clarify** the purpose, mechanisms and scope of

	observational activities for which extensive medical data and reporter causality are lacking and follow-up is not possible. Point (b) is also not consistent with point (a): If the minimum requirement is that "*a causal relationship cannot be excluded*", the threshold is much lower than the requirement that there "*must be at least a reasonable possibility for a causal relationship*". In general, companies apply a conservative approach in the assessment of causality for cases with missing reporter causality. However, their decisions should be based on medical and scientific assessment e.g. events or outcomes which are expected in high morbidity or mortality populations could be assessed as non-suspected in the absence of a reporter causality. To consider all cases with missing reporter causality as 'suspected' is very problematic. The article should recognise the constraints that apply with regards to the collection of non-serious adverse events from post-authorisation studies and clinical registries, as currently recognised in Volume 9A, and be amended to allow the MAH to provide a causality assessment in such situations, thereby allowing for 'unrelated' events to be excluded from a need for expedited or periodic notification. Otherwise, this new requirement will lead to significant over-reporting of relatively low-value cases, particularly if the MAH is not given the legal means to use medical judgment in assessing the possible causality in the absence of a treating physician's attribution statement. If the proposed changes opposite are rejected, please consider that the definition of causal relationship proposed in this article	ADR reporting by patients, which appears to be new and is currently not a regulated requirement within the EU. We strongly recommend that the paradigm rely only on HCP causality assessments, as patients are not qualified to make such evaluations.

	is not wholly consistent with that provided within ICH E2D and the understanding that a 'relationship' requires facts, evidence or arguments suggesting a causal relationship. Finally, litigation and class action cases and their handling should be clearly separated from other non-HCP cases.	
Page 22 Article 101e.1	With regards to "*The MAH shall accept reports of adverse reactions electronically*", it is unclear if this applies only to ADRs from regulators or from the public also. Is the intent that MAHs create on-line reporting tools for the general public and educate them in how to perform data entry?	**Please clarify** the scope of this proposed requirement, and what role, if any, ICH E2B standards have in this process.
Page 23 Article 101e.1	This article proposes that reports of adverse reactions should be collated in one point within the community. Please clarify what "*collated at one point within the Community*" means. Does this mean collated electronically in a single database? Will the collation occur via submission to the EudraVigilance database or does the MAH have additional responsibilities to collate data themselves, particularly with regard to adverse events occurring in third countries? Please note that the current regulatory requirement is for "*all suspected adverse reactions…..collected and collated in order to be accessible at least at one point within the Community*." If the reports are now required to be collated at one point within the Community, as opposed to simply being accessible, this would have a significant impact on the organisational structure of pharmacovigilance systems in many companies. Overall, these reports should be accessible at one point within the Community: where they are collated would seem to be	**Amend to:** *"These reports shall be ~~collated at one point~~* ***accessible via a single point*** *within the Community."*

	immaterial. What if regulators from other non-EU regions were to ask for the same? How would this be managed?	
Article 101e.2 Page 23	This article proposes that MAHs shall submit electronically to EudraVigilance all adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community within 15 days of receipt. This proposal is ambiguous and impractical, and represents a major change in reporting obligations that will create undue burden for industry and EudraVigilance and provide minimal benefit to the protection of public health, particularly that relating to the expedited notification of non-serious ADRs. Whilst we support the requirement to submit all serious ADRs within 15 days of receipt, whether 'expected' or 'unexpected', thereby obviating the need to assess each ICSR against multiple national SmPCs, it is not clear what public health benefit arises from imposing a requirement to submit all non-serious ADRs within 15 days of receipt. We can understand why these should be populated in EudraVigilance for signal detection purposes but it is not at all clear why expedited reporting has been extended to non-serious reports that occur in the Community. The proposal represents a major process change for MAHs that would negate the purpose of conducting case triage to process and transmit the most important cases first. Many MAHs currently structure their case handling activities so that priority is given to ICSRs that require expedited notification.	Please **amend to:** *'2. Marketing authorisation holders shall submit electronically to EudraVigilance, no later than 15* ***calendar*** *days following the receipt of the report, all* ***medically confirmed serious*** *adverse reactions that occur within and outside of the Community.* ***Non-serious adverse reactions arising from within the Community, and notified to the MAH as 'spontaneous' post-marketing reports, shall be submitted electronically to EudraVigilance on a periodic basis (no less than once every 3 months), or upon specific request by a competent authority.*** ***Competent authorities shall submit electronically to EudraVigilance, no later than 15 calendar days following the receipt of the report, all serious adverse reactions that occur within and outside of the Community notified to the competent authorities from other sources. Analogous non-serious adverse reactions shall be submitted electronically by the competent authorities to EudraVigilance on a periodic basis (no less than once every 3 months)."***

	Consequently, it is usual for the data management of non-serious ADRs to take somewhat longer than serious ADRs, recognizing that (in general) non-serious ADRs have less potential public health consequences than serious ADRs. Therefore, it seems both unreasonable and impractical to impose a requirement that non-serious ADRs are notified within 15 days of receipt. Furthermore, the proposal will restrict the ability of MAHs to managed fluctuations in workload, as there will no longer be any flexibility to postpone non-serious processing for short periods of time when workload is high. Does this apply to all non-serious ADRs, irrespective of origin (including post-authorisation studies), or does it only apply to those from spontaneous post-marketing reports? It should be clarified that this requirement will only apply to non-serious 'spontaneous' post-marketing ADR reports: it should not apply to non-serious ADRs from clinical trials on marketed products, which are subject to Directive 2001/20/EC, or to non-serious ADRs from post-authorisation safety studies or other 'solicited' sources, which Volume 9A requires to be presented in the respective end-of-study reports and should not be subject to expedited reporting requirements. Furthermore, expedited reporting should be limited to serious adverse reactions that have been medically confirmed. Otherwise, it should specify that it includes spontaneous reports from all sources, including consumers. Please clarify whether it is 'working' or 'calendar' days in no "*later than 15-days*", rather than allowing MAHs to assume that it is calendar days	

	Extension of the periodic submission of non-expeditable reports currently required for centrally approved products (as presented within Volume 9A) should suffice. Concentrating resources in quick shipment of non-serious events may be less productive for pharmacovigilance than using the resources freed up by the simplification of reporting to perform follow-up activities on information with greater impact on the public health. Finally, considering that reciprocal requirements currently exist for competent authorities to notify serious ADRs to MAHs, this reciprocal requirement should be maintained with regards to the new provisions. The practical consequences should be borne in mind when considering the timelines for electronic notification of non-serious ADRs.	
Page 23 Article 101e.2	With regards to the statement "*These reports will be made available to the Member States through EurdaVigilance*", does this requirement mean that no additional reporting to national competent authorities is needed, since they will all have access to the EudraVigilance database?	**Please clarify** this requirement.
Page 23 Article 101e.2	There is a risk of duplicate reporting to EudraVigilance, since the competent authorities should send their cases to EudraVigilance and to the MAHs who in turn may report the same cases to EudraVigilance. It is not clear from the text how duplicates will be avoided if both the Member States and the MAHs will submit to EudraVigilance.	**Amend to:** "*MAHs shall submit…, all* ***serious*** *adverse reactions that occur in the community* ***except cases received from the Competent Authorities*** *and all serious reactions that occur outside the Community.'*

Page 23 Article 101e.3	With regards to reporting by HCPs and patients via websites linked to the EU medicines safety web-portal, this will only increase the background noise and make it more difficult to identify relevant information and true signals. Moreover, such a system can easily be distorted or even brought to a collapse by fake reports sent by hostile individuals or groups, so it is open to sabotage. It will be impossible for the MAH and the authorities to 'find the needle in the haystack'. Receiving more data does not automatically mean better data, especially if it becomes impossible to find out the relevant data (garbage in – garbage out). The timelines for the Member States to capture the cases collected by them is not specified. It should be the same as those defined for industry to facilitate signal detection by the responsible MAH(s). The competent authorities should validate any reports received from patients and healthcare professional to avoid anonymous (and possibly bogus) reporting. Reports of adverse reactions that were submitted to the MAH by the Member State (and which also were sent to EudraVigilance) should not be submitted to EudraVigilance by the MAH as well, as this will lead to an abundance of duplicate reports on EudraVigilance. Provisions need to be in place to prevent such duplicate reporting to EudraVigilance.	**Amend to:** *'3; The Member States shall record all adverse reactions that occur in their territory which are brought to their attention from healthcare professionals and patients. Member States shall submit electronically to EudraVigilance all of the reports from healthcare professionals within 15-calendar days following the receipt, which meet the notification criteria in accordance with the guidelines referred to in Article 101b.* *To facilitate the reporting of suspected adverse reactions by healthcare professionals and patients each Member State shall accept reports of adverse reactions via their websites; ~~which~~ **reports from healthcare professionals** shall be linked to the European medicines safety web-portal referred to in Article 101i'*
Page 23 Article 101e.3	For sake of completeness and signal detection, medication errors associated with suspected adverse reactions should also be submitted to EudraVigilance.	**Amend to:** *"The Member States shall ensure that reports of medication errors **associated with suspected adverse***

		reactions *brought to their attention in the framework of adverse reaction reporting for medicinal products are* ***submitted to EudraVigilance and*** *made available to any national competent authorities for patient safety within that Member State."*
Page 23 Article 101e.5	The proposal that EMEA assumes responsibility for monitoring the worldwide literature to avoid duplicated effort is commendable and laudable in its intent to reduce administrative burden but do not underestimate the workload involved (especially in relation to the benefit gained). But, in practice, this will only benefit companies which market solely within Europe or with minimal presence outside the EU as there will still be a responsibility for larger multinational companies to conduct these searches for products which are not only approved in Europe but also in other regions such as North America or Japan. The only advantage in continuing with this proposal would either be to limit the search to innovator or generic products approved only in the EU (and in countries outside the EU which do not require submission of literature case reports) or to obtain agreement from FDA, Health Canada, MHLW etc that the literature searches undertaken by EMEA, with cases entered onto EudraVigilance and thereby accessible to the MAH for further submission to other authorities as appropriate will be considered an acceptable means to these authorities of fulfilling global literature search responsibilities for those products approved in the three ICH regions. If MAHs do not have access to the reports documented in EudraVigilance connected to EMEA literature screening, then	**Amend to:** "5. *The Agency shall monitor medical literature for reports of adverse reactions to* ***mature, off-patent*** *medicinal products for human use authorised or registered in the Community. It shall publish the list of publications subject to this monitoring, and it shall enter into EudraVigilance relevant information from the identified literature* ***that will then be made available to the responsible MAHs****.* *The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the conduct of medical literature monitoring, entry of relevant information into EudraVigilance,* ***and the access of MAHs to the information entered to EudraVigilance regarding their products."***

	they would have to go on with their own parallel literature screening for PSUR and signal detection purposes, and to meet the regulatory needs of non-EU authorities. Indeed, it should be clarified whether the MAH is still responsible for monitoring local medical literature for safety surveillance purposes or will this become the responsibility of the competent authority of the Member States? If any other cases are detected by the MAH (e.g. literature cases from third countries detected in publications not monitored by the Agency), will the MAH need to enter them in EudraVigilance? Hence, the cases screened by the Agency should be made available to the MAHs. Otherwise, the proposal would simply be a waste of public money and resources. The proposal for EMEA to scan and data enter case reports from the published literature could be limited to mature, off-patent products. There are several questions that need to be answered: • Will the MAH be relieved of the primary responsibility of performing literature searches for products licensed in the EU? • Will the list of publications include all relevant global publications, and if not, will the MAH be obliged to monitor any publications not included on the list? • Will the EMEA review non-English language publications and publicise the list of publications reviewed and any modifications that may occur from time to time? • Will the MAH have access to their products' cases in	

	Eudravigilance? The timelines for data entry will need to be clearly defined for the Agency as well as for the Member States in the guidelines referred to in this article.	
Page 23 Article 101e.5	The benefit of "*major cost savings for industry and national regulators*" anticipated by the Commission in Section 3.2.6 can only be achieved if there is an ongoing dialogue between industry and the Commission about the needs of industry - which in this context are in large parts driven by the requirements to comply with world-wide regulatory requirements for submission of literature articles. In this context, initiatives such as the FDA/European Commission 'Transatlantic Administrative Simplification Workshop' recently held in Brussels should be mentioned positively. There, the clear need for administrative simplification through transatlantic and international collaboration and harmonization was highlighted. The spirit of such initiatives should be considered at this point in time, i.e. at the stage of public consultation on the new legislative proposal, in order to ensure true, and not only anticipated, savings for all stakeholders. In the context of the above, the following needs detailed consideration: - transparency on types of searches or search profiles used - transparency on biomedical databases searched - the source of the literature article	**Amend to:** *'The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the conduct of medical literature monitoring and the entry of relevant information into EudraVigilance* **giving consideration to the global nature of literature case processing and related international administrative alignment.'**

	- identification of duplicates - type of articles considered for placement onto EudraVigilance - handling of articles in 'local language' translations - periodicity of searches performed - provisions made to ensure timely literature article availability - criteria to determine literature case validity - management of 'Received Date(s)' - case formats and alignment with major international regulatory agencies	
Page 24 Article 101f.1	The first paragraph of section 3.2.7 in the 'Key proposals' is not reflected in this article i.e. "*no PSURs for old established products*". This article should define clearly for which products PSURs need to be prepared.	**Please clarify** if there will be no requirement to submit PSURs for old established products.
Page 24 Article 101f.1	PSURs are dedicated to safety only and should not contain a full benefit-risk evaluation. It should not be necessary to re-evaluate the benefit-risk profile of a medicinal product if there is no change in risk. If specific EU PSURs have to be prepared under a format different from the one described in Volume 9A, please clarify the format to be used.	**Amend to:** *'Marketing authorisation holders shall submit periodic safety update reports to the Agency.* ***In case of change in the safety profile of the medicinal product, this report should*** *contain a scientific evaluation of the risk–benefit balance of the medicinal product on the basis of all available data'.*
Page 24 Article 101f.1	**With regards to the statement** "*Marketing authorisation holders shall submit periodic safety update reports to the Agency …*", does this mean that it will not be necessary to	**Please clarify**.

	submit PSURs to individual national competent authorities?	
Page 24 Article 101f.1	This article indicates that PSURs should contain "*all data*" on sales and "*any data"* on prescription volume. This would legally oblige inclusion of huge amounts of information, which may not always be practical or of added value. Please clarify the rationale for this requirement and consider amending it to only include relevant data.	**Please clarify the rationale, and amend to:** '*Periodic safety….shall also contain* ***relevant*** *data relating to the volume of sales……. and any* ***relevant*** *data in possession of the MAH relating to the volume of prescriptions.'*
Page 24 Article 101f.1	It is not clear from the text whether the PSUR review should be based on the model of the centralised procedure irrespective of route of authorisation.	**Amend to:** *"1. Marketing Authorisation Holders shall submit periodic safety updates reports* ***in accordance with the centralised procedure model*** *to the Agency..."*
Page 24 Article 101f.2	At present, the PSUR shall be submitted 60 days after the data lock point; the MAH may request before data-lock an extension to 90 days in case of extensive number of cases. It is important that this option remains possible under the new legislative framework.	**Please confirm** that current 60/90day timelines will be maintained.
Page 24 Article 101f.2c	A definition of '*immediately upon request'* is needed, otherwise please delete the word '*immediately'*.	**Amend to:** "*In the absence of specification pursuant to a) or b) above,* upon request or at least…
Page 24 Article 101f.2	With regards to the sentence "*Reports shall be submitted electronically*", this requirement should be clarified. Will such reports be electronically structured? Or should these reports be sent electronically using an available format such as PDF? No paper copy should be required in the event of electronic submission.	**Please clarify** the requirement and provide guidance on format for electronic submission of PSURs.
Page 24	Generic products are meant to be generally exempted, except "*products of biological origin*". Does this mean that the	**Delete:** ~~3. Unless other requirements have been laid down as a~~

Article 101f.3	Commission believes that no PSURs need to be submitted for any 'ordinary' generics (i.e. non-biosimilars)? If so, this may not be in the best interests of patient safety. Does this exemption also apply to the originator of the off-patent product, which provided the basis for the generics? If not, this would mean that the originator does not only have to bear the burden of the patent-loss, but also the pharmacovigilance burden for the entire molecule and thus for the other companies. What, if the originator decides to stop marketing his product as a result of the patent-loss and generic competition? Then no PSURs for this molecule would be submitted anymore. This is a clear breach of the basic rule to impose the same obligations to all market partners, which is a ground rule for fair competition. Furthermore a different composition of the excipients might lead to a different safety profile of the generic product which would not be documented and assessed in a PSUR anymore. What is useful is to abolish the short fixed timelines (every three years) for active ingredients where no major problems can be expected.	~~condition for the granting of the marketing authorisation, the requirements of paragraphs 1 and 2 shall not apply to products authorised in accordance with Articles 10, 10a, 10c, 13 t o 16 or 16a to 16i of Directive 2001/83/ EC.~~
Page 24 Article 101f.3	We support the concept of linking PSURs to the risk management planning process and proportional to the extent of knowledge about the safety of an individual product, particularly if this involves discontinuation of the need to compile PSURs for well-established products. However, the wording in this paragraph implies that this	If this paragraph is not deleted (as suggested above), **add:** *"**This derogation shall also apply to the reference medicinal products named in applications for marketing authorisations granted in accordance with Article 10."***

	principle applies to generic products, but not to the corresponding reference product i.e. it appears to be a restrictive interpretation of the key proposal detailed in section 3.2.7 “no PSURs for old established products”. Assuming that there are no compelling reasons that the reference product should be treated any differently, then it should be clarified that the same standards also apply to the reference product. This paragraph should not be based only on application types but also should apply to established products for which the Committee of Pharmacovigilance considers that the knowledge about safety of the product is well established. Also, generic products should not be systematically exempted from the PSUR submission. Indeed, the manufacturing process may have an impact on the quality, safety, efficacy of the product and it could be important to monitor the safety of “new” generic products in a more active fashion than for some patented products.	
Page 24 Article 101f.4a	The scope of products for which the Committee on Pharmacovigilance will decide the dates for PSUR submission should be clarified as the word ‘certain’ is ambiguous. Since the PSURs are intended to be prepared globally for all the regulatory authorities, the reference date for new or original products should also take into consideration the international birth date in accordance with the ICH guidelines E2C and E2C(R1) adopted by the Commission. This is already the case as per the Volume 9A. Going back to the EBD only will create the need for different cut-offs for different countries, i.e. multiple documents with slightly different data sets. This would be very resource intensive, would make	**Amend to:** *‘The Committee on Pharmacovigilance referred to in Article 56(a) a of Regulation EC(No) 726/2004 may determine the European reference dates and frequency of submission of periodic safety update reports for certain medicinal products* ***taking into consideration the international birth date of these products****.’* **Please clarify** the scope of this article.

	international cooperation and information sharing on safety matters more complex. The current rule relating to use of the international birth date should be kept. Medicinal products registered via MRP/DCP or nationally are not in the scope of this article. Why not? The Committee should leverage on the Head of Agencies initiative and the list of reference dates that have been agreed between the national authorities and the MAHs, as published on the HoA site. Starting a new initiative with an independent harmonization effort would be a duplication/repetition of work. Changing what has been agreed so recently would create unnecessary confusion and rework.	
Page 25 Article 101f.4a	"…*active substance*…" should be replaced by the commonly used "…*active pharmaceutical ingredient*…".	**Amend to:** "*For the purpose of this provision, The European reference date for products containing the same* ***active pharmaceutical ingredient*** *shall be…"*
Page 24 Article 101f.4b	The creation of an additional listing with potentially differing or conflicting dates should be avoided where a respective listing is already in existence.	**Amend to:** **"*Unless already available through the listings of harmonised birthdates*,** *the Committee shall draw up…"*
Page 24 Articles 101f.4c and 101f.4g	The description of procedures for submission of requests to the Committee is vague. This section should be clarified concerning function and responsibility in relation to Member States. The rationale and validity of (g) needs to be clarified. Should this be included in the legislation, especially as the frequency of meetings may change over time?	**Please clarify** the procedure.

Page 24 Articles 101f.4e and 101f.4f	The review process for PSURs should be modelled on the current process available for Centralised Procedure products, which allows adequate time for discussion and interactions between the MAH and Regulators. We would support that conclusions of PSUR assessments and recommendations for changes of product information are published, provided that this is done in lay language adapted to the audience. Such communications should be made available to the applicable MAH when posted. The recommendations would then be implemented in the MA via a minor variation (Type IA immediate change according to the new Variation regulation proposal).	**Please clarify** these proposals to take into account the points raised.
Page 24 Article 101f.4f	The proposed timeline for the assessment of PSUR is not in line with the current practice (60 days). The proposed timescale of 90 days is too long and should be reduced in line with the current 60 days.	**Amend to:** "*The Member State or rapporteur responsible for the periodic safety update report assessment shall produce an assessment report within* ***60*** ~~*90*~~ *days of receipt of …*
Page 24 Article 101f.4f	The time given to the MAH to comment on the assessment report of PSUR is too short (30 days). In some instances, some request would need more time for proper answer.	**Add:** "**When needed, extended deadlines to answer should be agreed between the MAH and the MS/rapporteur and the committee."**
Page 24 Article 101f.4h	The MAH can respond to assessment reports and the ultimate outcome may be different from what was set forth in the initial assessment report. For example, the assessment report could suggest a change to Reference Safety Information but if the MAH responds to successfully defend a position not to make the change, the information would have been made public but	**Amend to:** ***"A summary of*** *the* ***final*** *assessment conclusions shall be made public including any recommendations for the product information by the Agency via the European medicines safety web-portal referred to in Article 101i."*

	the RSI change would not have been warranted – therefore the public receiving the information at this stage is premature. It is important that only the final assessment report is made public, after MAH response is received and taken into consideration. It may be reasonable to make public the assessment conclusions (but not the full PSUR assessment report) following adoption at the meetings of the Committee on Pharmacovigilance. Therefore, only a summary of the assessment conclusions, written to be understandable by patients and members of the general public should be made public. It is important that information released on medicinal products be well understood by the patients who take these medicines. Also the principles on deletion of commercially confidential information should be respected. Consideration should be given to utilising the current European Public Assessment Report (EPAR) process to communicate these assessment conclusions. The EPAR is intended to be updated throughout the authorisation period as changes to the original terms and conditions of the authorisation are made, and the assessment conclusions could be included in the EPAR for a medicinal product. Further, EPARs contain a summary written in a manner that is understandable to the public. This may warrant the extension of EPARs, or an equivalent, to medicinal products not authorised via the centralised procedure.	
Page 26 Article 101g.1	The 'serious concerns' that would result in the requirement to conduct a PASS need to be defined. It is essential that there is consistency in implementation of this requirement - examples	**Please define** the term 'serious concerns'.

	should be given to establish common grounds as to what would deserve an ad hoc PASS across evaluators/agencies.	
Page 26 Article 101h	The proposal to codify the conduct of non-interventional post authorisation safety studies is welcomed. However, since the term is not defined in the Directive, this leads to ambiguity. It is proposed that the definition provided in Directive 2001/20/EC is used.	**Please define** the term 'non –interventional study' as follows: ***"Non-interventional study: The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data."***
Page 26 Article 101h.1a	We fully agree with the Commission's position 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 pursues a scientific objective, as opposed to the prohibition set out in the proposed Article 101h1.a) that focuses on a role related to promoting medicines (note: sometimes a study can serve both purposes, simply through the recruitment of local key opinion leaders to conduct a truly scientific study, and this should be accepted). We also believe that imposing a positive requirement will reduce the risks of different, or even potentially conflicting	**Amend to:** *"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."***

	interpretations, at national levels.	
Page 26 Article 101h	It would be helpful if the Directive could specify the requirements for the management of PASS that are to be conducted in non-EU countries. Such studies can form part of the Pharmacovigilance Plans for products authorised within the EU, with direct relevance to the safety of European patients administered these medicinal products.	**Please clarify** the requirements for PASS conducted in non-EU countries.
Page 26 Article 101h.1a	Clarification is requested as to whether the intent of the wording is 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.	**Please clarify** if Investigator Sponsored Studies are included within this provision, or outside its scope.
Page 26 Article 101h.1c	This requirement, that in the current volume 9A is limited to PASS that are part of an RMP or are requested by EU competent authorities, now seems to extend to any PASS, whereas amendments do not need any approval, for any type of PASS. It would seem to be more appropriate to maintain submissions for draft protocols and amendments for PASS requested by competent authorities (or within RMPs), instead of a review of all draft protocols.	**Amend to:** ***"When a post-authorisation safety study is requested by a competent authority,*** *a draft protocol shall be…"*
Page 27 Article 101h.1d	The proposal states that it is at the discretion of the Committee on Pharmacovigilance or the national competent authority to determine whether or not a letter of objection is issued. An	**Amend to**: *"d) In the absence of a letter of objection… …the marketing authorisation holder shall be informed in*

	appeal procedure should be available to the MAH in the case of objection. In the event that a study is considered to fall under the scope of Directive 2001/20/EC, the rules of the Directive 2001/20/EC should apply and the Committee for Pharmacovigilance written approval should not be required.	*writing with detailed grounds. In the event* ***that the study is considered to promote the use of a medicinal product,*** *the study shall not commence until the competent authority or the Committee has given its written approval. "* Please provide details of an appeal procedure for cases where a letter of objection is issued.
Page 27 Article 101h1e	'*The competent authority or the Committee, as appropriate, may give a recommendation on the submitted protocol within 60 -days*' should be reworded for clarity.	**Amend to:** "*e) The competent authority or the Committee, as appropriate,* ~~*may*~~ ***shall have a maximum of 60 days from the date of receipt of the protocol to*** *give a recommendation on the submitted protocol."*
Page 27 Article 101h.1f	We support the proposed notification-only process for protocol amendments. However, does this mean that MAHs may enact the amendments with immediate effect?	**Please confirm** that the notification-only process allows for immediate implementation of any proposed change to the protocol.
Page 27 Article 101h.1h	The submission of final study reports should not be specified in the protocol as often studies involve countries outside the EEA who might have different requirements. It is recommended that summaries of study reports are submitted to the competent authority with 12 months of 'last patient last visit' consistent with the Directive 2001/20/EC. To whom shall the study report be submitted and what should the protocol specify with regards to ADR reporting?	Amend to: *'h)* ~~*The submission of final study reports and*~~ *The reporting of adverse reactions from the studies shall be specified in the study protocol. Summaries of final study reports should be submitted to the competent authority with 12 months of 'last patient last visit.'*
Page 27 Article 101h.1j	The MAH should always give its agreement for the publication of abstract, and not only for the publication of an amended abstract.	**Amend to:** "j) *In addition to any reporting requirements in the study protocol, the marketing authorisation holder*

	Concerning the disclosure of information of these non-interventional post-authorisation safety studies, it would appear based on the current proposal that this will occur on a case-by-case basis. Clarification is required on the principles to be applied by the Committee to decide whether information should be released. Also based on the proposal, information on these studies would be disclosed only when the study will be conducted in more than one Member State. Will the national competent authorities have the same rights for single-country studies?	*shall submit an abstract of the study results to the Committee.* ***After the agreement of the marketing authorisation holder,*** *the Committee may decide that the abstract is made public via the European medicines safety web -portal referred to in Article 10 1i or,* ~~*after the agreement of the marketing authorisation holder,*~~ *may decided that an amended abstract shall be made public."* **Please clarify** the principles for selection of studies for public disclosure.
Page 27 Article 101h.1k	The Committee should consult the MAH before making its final recommendation publicly available. In addition, we suggest that any publicly available recommendations for product labelling be provided on the website only after there is agreement between the EMEA and the MAH on the content.	Amend to: "*Based on the results of studies* ***and after consultation of the marketing authorization holder,*** *the Committee may make recommendations for the product information and these shall be made public via the Agency web-portal* ***after the changes are finalised****."*

CHAPTER 5		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 28 Article 101i.1(c)	All requests for patients to report adverse reactions should also include a recommendation for them to consult their physician.	**Amend to:** "(c) *Information about how to report …and marketing authorisation holders.* ***Patients should be reminded of the need for them to consult their physician should they experience adverse reactions."***

Page 28 Article 101i.1(d) and Article 101i. 2	It is being proposed that copies of Risk Management Plans are placed on a European medicines safety web-portal (Article 101i.1) and on national safety web-portals (Article 101i.2). Consideration needs to be given to the fact that Risk Management Plans are written as part of the marketing authorisation process, often containing complex technical data and information (e.g. results of preclinical studies), with the Competent Authority as the primary customer. Hence, they are not written in a manner best suited for the general public, such that if presented in this manner they could lead to misunderstanding and alarm amongst patients being prescribed the medicinal product. We support the idea that there should be public transparency with regards to risk management planning, as the public have the right to know about the risks associated with the medicines they are being prescribed, and the measures being taken to assess and/or minimise those risks. However, this information must be presented in a reader-friendly manner that allows the public to readily understand the information being shared, and that does not lead to unnecessary misunderstanding and alarm. If the purpose is that of increasing transparency, summaries providing essential information in an understandable language would seem to be more appropriate than full documents. One such example is the practice now adopted by the French Agency	**Amend 101i.1d to:** "(d) *Agreed **patient-oriented summaries** of risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with Regulation (EC) No726/2004.* ***In agreement with the responsible marketing authorisation holder, confidential information will be deleted from the plan before it is made publicly available.*** **Amend 101i.2a to:** *"(a) Agreed **patient-oriented summaries of** risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with the procedures of this directive."*

	(Afssaps), whereby a summary of the Risk Management Plan is provided on the Afssaps web site in a patient-oriented manner. Consideration should be given to utilising the current European Public Assessment Report (EPAR) process to communicate the relevant information contained within risk management plans to the public. The EPAR is intended to be updated throughout the authorisation period as changes to the original terms and conditions of the authorisation are made, and relevant information contained within a risk management plan could be included in the EPAR for a medicinal product. Further, EPARs contain a summary written in a manner that is understandable to the public.	
Page 28 Article 101i.1f	It is proposed that a list of MAH qualified persons is provided on a publicly accessible European medicines safety web-portal. We have strong objection to this proposal, for the following reasons: 1. The rationale for making QPPV details public is not clear and appears disproportionate – the QPPV acts as a single contact point for the competent authorities and the Agency on a 24-hour, not the general public. Therefore, who is the list directed at, and why? 2. It is a violation of the privacy of all QPPVs. 3. Public release of the identities of QPPVs has serious personal security implications and may	**Please delete** this proposal.

	expose QPPVs to unwarranted attention from individuals with harmful intent (e.g. animal rights activitists). The personal safety of QPPVs should not be compromised by posting information that has no direct benefit to the public health. In this context, applicable directives on the protection of individuals with regard to the processing of personal data and on the free movement of such data should be re-considered and the potential consequences of this proposal should be re-evaluated.	
Page 28 Article 101i.1i	We have concerns regarding the proposal of making public information on "*the initiation of the procedure of Article 101k, the substances or products concerned and the issue being addressed*," while the issue is still under active review by the Committee of Pharmacovigilance. Indeed unbalanced presentation of safety signals outside the context of potential benefits may have potential unintended consequences such as having patients, who in some cases may stop medication on their own without consulting a physician. Furthermore, public hearings are not helpful, since they are very likely to become a 'show events' rather than scientific discussions, with presentations given to the public rather than to the scientific community.	**Please delete** this proposal.
Page 27 Articles 101h & 101i	With regards to the proposed European medicines safety web-portal, EFPIA supports the goal of the portal to promote transparency and timely	A process of consultation with the MAH is <u>critical</u> to ensuring that the information on the web portal remains consistent and synchronised with the information in the

	communication of relevant drug safety information. However, careful consideration must be given to the potential unintended consequences that could result from posting product risk information and recommended changes to product information prior to appropriate review and discussion of that information between the competent and the MAH. The proposed Articles 101(h) and 101(i) refer to web posting of the competent authority's assessments of PASS and PSURs and recommendations for changes to product information, and in Article 23 it is proposed that the MAH must ensure the product information is kept up to date in light of the assessment conclusions posted on the web portal. These provisions could imply that each isolated risk assessment would be made public with an expectation that the same assessment will be reflected in the updated product information. What is missing is an assurance that, prior to web posting, the assessments will be discussed with the MAH to ensure consideration of the appropriate label change as well as proper context for an accurate public statement regarding the product's risks. A process of consultation with the MAH is critical to ensuring that the information on the web portal remains consistent and synchronised with the information in the product label and patient information. In the absence of such a consultation process, the risk information on the web portal could have negative public health consequences and lead to confusion among healthcare	product label and patient information.

	professionals and patients.	
Page 27 Article 101i.1h	Publication of PASS protocols in addition to public abstracts is not considered to be of additional value.	**Amend to:** *"h) ~~Agreed post-authorisation safety study protocols,~~ The public abstracts of **post-authorisation safety studies** and any…"*
Page 28 Article 101i.3	What is meant by "…*a marketing authorisation holder has the intention*…"? For clarity, please focus on withdrawals due to safety concerns as some products are withdrawn for economic reasons.	**Amend to:** " ~~As soon as~~ ***Before*** *the holder of a marketing authorization* ***makes*** *a public announcement relating to important information on pharmacovigilance concerns including product withdrawals* ***due to safety concerns*** *and major restrictions to the use of a product, he shall give notification to the Member State competent authorities, the Agency and the Commission. "*
Page 28 Article 101i.5	The EMEA and PV Committee should drive the communication of risk management plans to ensure consistency on MS Agency websites and also for products under intensive monitoring. '*All reasonable efforts'* to agree common safety messages does not go far enough, common safety messages should be agreed by all member states.	**Amend to:** "….the Member States shall ~~make all reasonable efforts to~~ agree common safety messages…"
Page 29 Article 101i.6	The obligation to consult the MAH in relation to information that is to be published and which may contain confidential information should be made clearer, in order to ensure that the MAH has the chance to protect its legitimate commercial interests and also any personally confidential information e.g. full names and addresses.	**Amend to:** '*When the Agency or national competent authorities make information referred to in the previous paragraphs public, it shall consult the MAH in advance of the public disclosure to ensure that any information of* ***a confidential*** *nature shall be deleted, unless its public disclosure is necessary for the protection of public health.'*

Page 29 Article 101j	The purpose and intent of the list of products under '*intensive monitoring*' should clearly be communicated to the public. Such a list will only lead to a stigmatisation of those products and could well have negative impact on patient compliance; patients may get concerned about the listed products and may mistrust their doctor's opinion with regards to the safety of the prescribed medicines. Hence, such a list will not improve patient safety; it might even be to the contrary, because patients may be subject to the misperception that a product not listed is particularly safe and can be consumed without hesitation or limitation. The currently ongoing Article 31 procedure on dopamine agonists or the recent market withdrawal of clobutinol demonstrates that it is a misperception to believe that only 'new' products are 'unsafe'. It would be useful to have two separate subgroups of the list rather than one: 1. List with newly approved substances 2. List with products that have potential risks/safety hazards/potential issues on public health Inclusion of products on these list need to be evaluated on a regular basis. This should be an EU list rather than by Member State. A mechanism to request a deletion from this list should	**Please clarify** the criteria for inclusion of a product in the list for intensive monitoring.

	be provided. Further clarification of the criteria to be used for determining which products require intensive monitoring should be provided in the text, as well as when and how the product is removed from the list. The inclusion of products on this list should also be linked to the risk management plan.	

CHAPTER 6		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Pages 29-31 Article 101k	The interaction with the MAH, particularly obtaining input from the MAH, should be defined.	Specify the involvement of the MAH in this process.
Pages 29-31 Article 101k	An appeals process should be defined so the MAH can provide its position.	Please provide an appeals process.
Pages 29-31 Article 101k	Clarification should be provided for medicines authorised in one Member State only, including the roles and responsibilities for the decision making process at the local HA, and industry involvement and consultation procedure before the final decision is taken and communicated	Provide clarification for procedures for medicines authorised in one Member State only.
Pages 29-31 Article 101k	It is important that a standard template is used across Member States for the communication to the public of the products' safety information, and that MAHs' websites do	

	refer to the same information.	
Page 29 Article 101k.1	The procedure should be initiated only in case of safety concerns. Moreover, it should be clarified to which products this community assessment will apply and if this replaces the current referral procedures. The MAH is not included in the distribution list of the information that the Member State should deliver to the Agency, the Commission and the other Member States. Typos on the last two lines.	**Amend to:** *"A Member State shall notify the other Member States, the Agency,* ***the Marketing Authorisation Holder(s)*** *and the Commission and shall thereby… "* Articles (a) and (e) should be read articles (e) and (f).
Page 29 Article 101k.1e	A legal basis should be created for the adoption of interpretative guidelines on the concept of 'serious deficiencies'. Before the initiation of the procedure under 101k on these grounds is published (see Article 101i), the MA holder should first have had an opportunity to respond to the inspection findings. The relation of this procedure with the infringement procedure as described in Commission Regulation (EC) No 658/2007 of 14 June 2007 is unclear. This would seem to be a second procedure run in parallel. It is also unclear how the described community assessment for the evaluation and discussion of safety concerns would also apply to matters of compliance.	**Add:** ***"The Commission shall, in consultation with the Agency, Member States and interested parties, draw up detailed guidance regarding the concept of serious deficiencies."***
Pages 29-31 Article 101k.1 e	Even 'serious deficiencies,' should not be a cause for public assessment. Information on compliance-oriented industry processes must be evaluated with participation of directly	

	involved stakeholders. Corporate competitive knowledge is not a matter for public disclosure, but should be the subject of continuous improvement.	
Page 29 Article 101k.2	This provision would perpetuate the current situation where some Member States can take different decisions regarding the medicinal product in question. It would be preferable to postpone any regulatory decision until a consensus is reached at the European level, e.g. by the Committee on Pharmacovigilance where the concertation is lead by a designated Member State to address the safety concern with the MAH. The MAH is not included in the distribution list of the information that the Member State should deliver to the Agency, the Commission and the other Member States.	**Amend to:** *"Where urgent action to protect public health is necessary, the Member State concerned* ~~*may suspend*~~ ***shall initiate an urgent procedure with the Committee on Pharmacovigilance in order to propose on a uniform approach in the Community regarding*** *the marketing authorisation of a medicinal product. It shall inform the Agency,* ***the Marketing Authorisation Holder(s)****, the Commission and the other Member States not later than the following working day."*
Page 30 Article 101k.4	**B**ullet 4 is missing!	**Renumber** this article accordingly (should be 1-11, not 1-3, 5-12).
Page 30 Article 101k.5	The MAH should be informed at the same time as all other interested parties. Information from the MAH should also be considered within this procedure.	**Amend to:** "*…. the Member State shall make available to the Agency* ***and the marketing authorisation holder*** *all scientific information available to it,* ***and any information provided by the MAH, r****elevant to the notification and any assessment by the Member State."*
Page 29 Articles 101k.6 & 7	If urgent action is needed to protect the public health, then information should be provided within calendar days, not working days. Relevant manufacturers should always participate when their products are discussed in a public hearing and offer their	**Please amend** to calendar days.

	analysis of the data. The current text simply 'allows' for participation of the MAH.	
Page 30 Article 101k.6	It is completely unacceptable that the MAH must rely on a public announcement to be aware that an Article 101k referral procedure has been initiated for one of their products. The MAH(s) should be actively informed of such activities directly, not passively through a web-portal. It is also too late to inform the MAH(s) at this stage i.e. at the time of the public announcement. For the sake of clarity and transparency, it would be preferable that the MAH is informed as soon as a Member State or the Agency considers any regulatory action. Any consideration on a regulatory action or public communication should be shared with the MAH(s) as soon as possible and timelines should be decided with preliminary consultation between the competent authority and the concerned MAH(s). In addition, no timelines are recommended for exchanging the information between the MAH and the competent authority or for the MAH to prepare the response to the safety concerns. Furthermore, we have concerns with regard to public information be made available on a potential safety risk that has not been assessed at this stage in consultation with the MAH. The risk for some patients to stop their treatment may be high and possibly in contradiction with the final regulatory action that will be taken on the medicinal product (i.e. 10(a) no further evaluation or action is required at	

	Community level).	
Page 30 Article 101k.6	The public is meant to be able to submit information 'relevant' to the procedure. What is the criteria for 'relevant'? This could lead to the EMEA being inundated with irrelevant data, but separating the information will be resource-consuming.	**Delete the proposal.** ~~Where a public hearing is to be held pursuant to paragraph 7, t he announcement shall include information on the public hearing and how marketing authorisation holders and the public can participate.~~
Page 30 Article 101k.7	The MAH should have an automatic right of involvement in a public hearing. There is the danger of a well-meaning public hearing to become a 'public trial'. What is the definition of 'participation' of the public? Is this meant to be just attendance or active 'participation' by making contributions? If only attendance/listening is meant, then this should be expressed as such. If the Committee on Pharmacovigilance has to hold a public hearing this should be properly organised with the participation of external experts designated by the Committee and the MAH in the areas of concern.	**Amend to:** *"Except when urgent action is required for the protection of public health, the Committee on Pharmacovigilance shall hold a public hearing on the matter notified.* ***Concerned*** *marketing authorisation holders* ***will be invited to participate****, and the public may attend by registering following the public announcement of paragraph 5. The Agency shall ensure that all those who register have the opportunity to attend either in person or through the use of web-based technology.* ***External experts can be designated by the Committee on Pharmacovigilance and the MAH to participate in the hearing."***
Page 30 Articles 101k.9 & 10	The new article 56(1)(aa) of Regulation (EC) No 726/2004 establishes the PV committee at the same level that the other existing committees and in particular that of the CHMP. We consider that it is important: • to define how the PV committee will interact with the CHMP • to better define the responsibilities of the PV Committee	

	beside the responsibilities of the CHMP in the decision making process. • to better define the scope of activities of this committee: For example, will this Committee of Pharmacovigilance assess the safety profile of the products during the review of a market authorisation application as well as registered products or only registered products? Will this committee be competent to assess safety issues with devices?	
Page 3 Section 3.2.1 & Page 30 Article 101k.9	We agree that, at present, evidence-based conclusions about real safety issues and their mitigation are not comprehensively implemented across Member States, and that this represents a serious threat to the well-being of patients. This lack of consistency also creates a tremendous waste of scarce resources and time, adversely impacting regulatory agencies and industry. A stronger centralized process with binding conclusions can, however, be distorted and misused by politically-based opinions. To be effective – and to protect the public – the Committee must be given the obligation to make all pharmacovigilance decisions on the basis of evidence-based science using transparent processes that involve input from all relevant stakeholders. To ensure a robust system, further definition of the proposed role and scope of the envisioned Pharmacovigilance Committee, including interaction of the Committee with the CHMP and Member States, should be subjected to public consultation prior to implementation.	**Amend to:** "*The Committee on Pharmacovigilance**, using the best available evidence-based science and transparent processes involving input from all relevant stakeholders,** shall assess the matter notified and make a recommendation to the Committee for Medicinal Products for Human Use referred to in Article 56(1)(a) of Regulation EC (No) 726/2004."* In addition, please provide details of the role and interactions of the proposed Committee and ensure public consultation prior to implementation.
Page 31	Member States should implement risk minimisation actions	**Amend to:**

Article 101k.10d	in consultation with MAHs.	*"That the Member states need to implement risk minimization actions,* ***in consultation with Marketing Authorisation Holders,*** *and the nature of those actions."*
Page 31 Article 101k.10f	According to the draft detailed guideline referred to in article 6(1)(a) of the draft Commission Variations Regulation, update of safety information should be done through a Type IA immediate notification (New variations conditions No. 8).	Changes in the safety information should be subject to Type IA notification.
Page 31 Article 101k.11	It should be clarified what temporary measures the Commission may request.	
Page 31 Article 101k.12	A decision that no further evaluation or action is required is a decision as well. This should be communicated.	**Amend to:** ***According to paragraph 10 a) or 10 b),*** *the Commission shall adopt a ……*

CHAPTER 7		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 31 Article 101l.1a	We understand that this public register is limited to the delegation of the pharmacovigilance tasks by one Member State to another one or the Agency and is not intended to provide the detailed Pharmacovigilance Plan or Risk Management Plan.	
Page 31	There is no initial schedule specified here. Should the same apply for 1c as for 2(h) of this article?	

Article 1011.1c		
Page 31 Article 1011.1d	Will standard methodology be developed for monitoring the outcome of risk minimization activities by the Agency?	
Page 32 Article 1011.2	How far will the proposed delegation to Member States apply? Would delegation of any of the tasks imply extension of delegation of decisions on penalties? For example, would one Member State have the power to decide a penalty for a MAH that is a legal entity in a second Member State? Notwithstanding the legal basis of this delegation, it would be more practical to designate a 'lead' member state for each purely nationally approved medicinal product by the Committee on Pharmacovigilance.	
Page 32 Article 1011.2b/c	The role of the 'supervisory authority' for pharmacovigilance should be clarified.	**Please clarify** the role of the 'supervisory authority'.
Page 32 Article 1011.2c	Consideration should be given to aligning the supervisory authority Member State for centrally authorised products to the MAH's pharmacovigilance system, and not necessarily to the country of residence of the qualified person. This would address potential scenarios where the qualified person's country of residence, country of work location, and the country where the main pharmacovigilance site/headquarters is located all differ. Instead, consideration should be given to permitting the	**Please delete this requirement or amend to:** ***"c) The supervisory authority Member State shall be that in which the marketing authorisation holder's pharmacovigilance system operates, or the Member State in which the qualified person resides."***

	supervisory authority Member State to be that in which the qualified person resides, *or* that Member State in which the pharmacovigilance system has its main headquarters function. For pharmaceutical companies where the main headquarters function is located outside the EEA, the alternative would be the Member State in which the pharmacovigilance system has an office within the EEA that has pharmacovigilance responsibilities covering the EEA.	
Page 32 Article 101l.2d	Will Member States share pharmacovigilance data with the MAHs?	
page 32 Article 101l.2e	The monitoring responsibilites of the national competent authorities for products where no Reference Member State exists should be clarified in case the respective product is authorised in more than one Member State.	**Please clarify** the process for products that lack a RMS, with regards to the role of national competent authorities.
Pages 31-33 Article 101l.4	The opening paragraph assigns the responsibilities listed to the MA holder. However, (a) indicates that the qualified person shall be responsible for the establishment and maintenance of the pharmacovigilance system which shall cover the tasks listed in this paragraph – hence moving the responsibility from the MAH to the QPPV for items (b)-(f). This is not appropriate as (b)-(f) should remain the responsibilities of the MAH with QPPV oversight. The system of delegation whereby Volume 9A currently allows the QPPV to retain oversight of activities whilst not being directly involved should be	**Add:** ***"The qualified person for pharmacovigilance may delegate specific tasks to appropriately qualified and trained individuals, provided that the QPPV maintains oversight and overview of the safety profiles of all products."***

	maintained. The proposed wording could imply closer QPPV involvement than would be practicable in larger organisations.	
Page 33 Article 101l.4a	The phrase "*the competent authority*" is imprecise. It should be clarified whether it applies to the competent authority of the QPPV's country of residence or the competent authority of the country where the MAH resides.	**Amend to:** *".....The name and the contact details of the qualified person shall be notified to the competent authority* ***of the qualified person's country of residence*** *and the agency."*
Page 33 Article 101l.4d	It is unclear why it is incumbent on the MAH to monitor EudraVigilance and how far this requirement extends (e.g. to other products in same class?). What form of access will be provided - this task implies that the MAH will be granted full access to EudraVigilance and its tools for signal detection. How can signal detection be performed by the MAH on this dataset?	**Further clarification** is required on responsibility of MAH to monitor EudraVigilance for signals as such data are already available with the marketing authorisation documentation. **Amend to:** *"Monitor all available relevant data including data on EudraVigilance* ***to which an appropriate access shall be granted*** *for signals of new or changing risks and for changes to the risk benefit balance of the medicinal product."*
Page 33 Article 101l.4f	It is being proposed that reports of internal pharmacovigilance audits should be placed within the pharmacovigilance system master file. This is an unacceptable proposal, as such reports are confidential company information and there is no benefit to releasing them to an external audience. It should be sufficient to demonstrate that such audits are conducted; there should be no need to have to share the	**Please delete this specific requirement, or amend to:** "*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*~~ ***and file a report of each audit as an internal company confidential document."***

	results with the competent authorities, given that they have their own capability to conduct inspection programmes. Currently, most companies do not provide audit reports to the authorities, since there is a need to protect audit reports so that they can provide a true and accurate picture of the situation that was the subject of the audit. If these are required to be submitted to authorities, this may compromise the effectiveness of the internal audit process and undermine its usefulness as a compliance tool. However, it is reasonable to include details of a company's completed audit programme on the master file. In addition, evidence that internal audits of pharmacovigilance processes have taken place may also be considered for inclusion. What is the timing of 'regular' audits; is there a minimum number of audits per time period with which the MAH are expected to comply?	
Page 33 Article 101l.5	The concept of 'lead member state' for nationally approved medicinal products should be introduced here.	**Amend to:** "For medicinal products authorised in accordance with the provisions of Chapter IV, the tasks listed in paragraph 2(e), and (f) shall be performed by the **Reference** Member State **and by the lead member state designated by the Committee on Pharmacovigilance for the purely nationally approved medicinal products."**

CHAPTER 8		
Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Page 33 Article 101m	The scope of the "third country" in this article could lead to a misunderstanding as in the rest of the text the phrase "third country" includes all the non-EU countries, including the USA. Collaboration/communication with third parties (including WHO) should be strengthened to make sure safety requirements are consistent on a global level and that tracking systems are consistent inside and outside the EU.	**Please clarify** the scope of the phrase 'third countries' in this article.
Page 33 Article 101m	The Agency, as part of the pharmacovigilance system, should ensure full implementation of WHO policy on naming, especially with regards to glycoproteins. As mentioned in a letter from the Commission to the Heads of Agency, the Commission asks that national authorities take the necessary measures to ensure that the ADR reporting and pharmacovigilance system are in accordance with European legal requirements and in particular: • Includes, in the case of glycoproteins, a method to	

	link suspect adverse reaction reports to specific products (such as a unique product identifier); • Ensures that the prescribing doctors know which glycoprotein has been given to their patient in cases where reporting relies on prescribing doctors, and taking into account that substitution may occur in some systems at the level of pharmacies. **This is currently not addressed in the proposals.**	
Page 34 Article 101o	These measures need to be defined and processes need to be established to ensure equity in their application as well as defining any potential appeals process.	**Define** measures and establish processes to ensure equity in their application. **Define** an appeals procedure.
Page 34 Article 101p.1	Clarity is required regarding this section to show that it applies to products that have already been authorised.	**Amend to:** In the case of medicinal products authorised [<u>before</u> the entry into force of this directive],…..
Page 34 Article 101p.1	The EMEA (EMEA/CHMP/96268/2005) 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*" This information should be added to the Directive.	**Amend to:** *"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</u>***

	Amend (d)-(f) to (a)–(c).	***medicinal product*** *Any requirement shall:* *(a) be made in writing,* *(b) provide a detailed justification* *(c) include the timeframe for submission and agreement*
Page 37 Article 111.1d	With regards to this proposal for GMP Inspections, does this mean that pharmacovigilance is now in scope for every GMP inspection? Does a pharmacovigilance master file have to be located in every MAH manufacturing site?	Please clarify the scope of GMP inspections and the location of pharmacovigilance master file – recommend only one master file for all types of marketing authorization held at QPPV office as per comment above for Section 3.2.3.
Page 39 Article 111.8	This new paragraph should clarify the process for regarding issuing a MAH comment to the audit report prepared by the authority.	**Amend/Add** to the beginning of paragraph 8 as follows: *"**The competent authority of the Member State compiles a draft report on the audit results inclusive of all uncovered deficiencies and provides the MAH with the draft version. Within 6 weeks after receipt, the MAH may comment on the contents of the draft report. Subsequently, the competent authority compiles the final report which either takes the MAH comments into account or at least gives reference to dissenting opinions. All final PV inspection reports shall be sent by the Member States to the Agency and to the marketing authorisation holder**. If the outcome of the inspection…".*
Page 39 Article 111.8	The reference to Article 101n should be 101o.	**Amend to:** *"….in Article 101o."*
Page 39 Article 111.8	For sake of clarity, please define the phrase "*does not comply*". Does this apply to any findings, even if only minor, or only to the critical ones?	**Please define** "does not comply".

Page 39 Directive 2001/83/EC Article 116	The consideration of risk-benefit balance under normal conditions for use should be retained. Patients should not be denied access to a medicine as a result of people using the product outside of the authorised conditions of use. If the phrase 'under normal conditions of use' is not reintroduced in the text then the circumstances in which such action might be taken should be clearly defined instead.	Please **amend to** - *"The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken ~~that the product is harmful in normal conditions of use, or that it lacks therapeutic efficacy or~~ **that** the risk-benefit balance is not positive **under normal conditions of use,** or that its qualitative and quantitative composition is not as declared.* *~~Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product~~"*
Page 40 Directive 2001/83/EC Article 117 *'1. (a) The risk-benefit balance is not favourable'*	The consideration of risk-benefit balance under normal conditions for use should be retained. Patients should not be denied access to a medicine as a result of people using the product outside of the authorised conditions of use. If the phrase 'under normal conditions of use' is not reintroduced in the text then the circumstances in which such action might be taken should be clearly defined instead.	Please **amend to**: *(a) the risk-benefit balance is not favourable ~~under the authorised conditions of use~~ **under the authorised conditions of use***
Page 40 Directive 2001/83/EC Article 117 *'3. The competent authority may limit the prohibition to supply the product to new patients'*	The purpose of this new provision is unclear because the medical practitioners usually have the right to prescribe any medicine (notwithstanding possible difficulties in relation to their coverage by national health insurance policies) if they consider it is the right treatment for their patient. Under these conditions it is not clear how Competent Authorities can prohibit the supply of a product exclusively to new patients in an effective manner	Please **delete** 3.

Page 42 Article 18 (3)	It is proposed that the Member State where the company QP resides becomes the supervisory authority for pharmacovigilance. This assumes that the location of the company QP is static and that there is a constant organisational structure. This is not the case with many MAHs. If the Member State where the company QP resides becomes the supervisory authority for pharmacovigilance, a specific process would be required to allow for a change in supervising Member State if the company QP changed. It is recommended that this proposal be amended to detail that the Member State in which the legal entity of the MAH resides or the member State where the main pharmacovigilance system operates becomes the supervisory authority for pharmacovigilance. This would appear to be more stable and less subject to change.	**Amend to:** '3. *For the purposes of inspection the supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which* ***the main pharmacovigilance system operates, or the Member State in which the legal entity of the MAH resides t*** ~~*the qualified person responsible for pharmacovigilance resides'*~~
Page 43 Article 56 (1)	Replacing the Pharmacovigilance Working Party with a Pharmacovigilance Committee is supported. However, it is important that the role and responsibilities of the Pharmacovigilance Committee and its interaction with the Committee on Human Medicinal Products are defined. In addition, it is unclear which differences in mandate exist compared to the current PhWP. Which role will the CHMP maintain as far as patient safety is concerned ?	**Please clarify** the role and responsibilities of the Pharmacovigilance Committee and its interaction with the Committee on Human Medicinal Products.
Page 43	The purpose and scope of the proposed new text should	

Regulation (EC) No 726/2004 57(2)	be clarified. Based on EFPIA's review of the text it could be referring to two alternative interpretations. (i) The establishment of a list of all medicinal products authorised in the Community in which case the electronic submission of medicinal product information refers to the submission of defined information (e.g. product name, generic name, dosage form) to create this list. (ii) The provision of electronic submission of medicinal product information, where the term product information is the SmPC, Patient Leaflet, Packaging text etc. It is critical that the intent of this revision to the Regulation is clarified and the text is rewritten to more clearly reflect the proposed intent of the change to the Regulation. EFPIA has commented below on both interpretations and proposed changes in relation to both interpretations.	
	Interpretation 1: List of all Medicinal Products authorised in the Community The database already contains the list of medicinal products that have been authorised in the Community using the Centralised Procedure. The timings defined in the draft revised Regulation therefore refer to the other Community procedures and to the national procedures. It is EFPIA's position that the information on	Please **amend** to *"(a) by -/- (six-months after the entry into force of the directive) the Agency shall make public a format for the electronic submission of medicinal product information*; *(b) by -/- (eighteen months after the entry into force of the directive)* ~~*marketing authorisation holders*~~ ***National Competent Authorities*** *shall electronically submit to the Agency medicinal product information compliant with the format referred to in point (a) for all*

	medicinal products that have been authorised in the Community using Mutual Recognition, Decentralised and National procedures should be provided by the National Competent Authorities. The NCAs have the list of authorised products for the territory within their responsibility. It is EFPIA's position that Marketing Authorisation Holders should be given the opportunity to validate the list of medicinal products authorised in the Community before it is finalised and before it is to be made public. This approach was successfully applied to the list of medicinal products that have been authorised in the Community using the Centralised Procedure. Using this approach, the timings defined in points (a) and (b) of the revised Regulation will apply to the National Competent Authorities. In addition, Marketing Authorisation Holders will require a further 6 months to review and validate the lists provided by the NCAs. An additional point should then be included in the new Regulation. If the position is not accepted that the National Competent Authorities provide these data and hence Marketing Authorisation Holders are requested to provide the information on medicinal products that have been authorised in the Community, more time will be required to submit this information to the Agency. For large companies the activity to validate the list of information to be provided across all affiliates is a significant exercise. If MAHs are to be asked to supply this information according to an electronic format yet to be defined, longer than 18 months after entry into force of the directive will be required. In this case, the Regulation would need to read:	*medicinal products authorised or registered in the Community;* ***(c) by -/- 24 months after the entry into force of the directive, marketing authorisation holders in the community shall have validated the medicinal product information provided by the National Competent Authorities;*** ***(d)*** *from the date referred to in point (b)* ~~*marketing authorisation holders*~~ ***National Competent Authorities*** *shall notify the Agency of any new authorisations granted in the Community compliant with the format referred to in point (a)."*

	(*a) by -/- (six-months after the entry into force of the directive) the Agency shall make public a format for the electronic submission of medicinal product information;* *(b) by -/- (~~eighteen~~ **twenty four** months after the entry into force of the directive) marketing authorisation holders in the Community shall electronically* *submit to the Agency medicinal product information compliant with the format referred to in point (a) for all medicinal products authorised or registered in the Community.* *(c) from the date referred to in point (b) marketing authorisation holders shall notify the Agency of any new authorisations granted in the Community compliant with the format referred to in point (a).”* Finally, with respect to this interpretation of the proposed change to the Regulation, EFPIA is aware that **much of the information requested has already been provided by some MAHs to the EudraVigiliance Medicinal Product Database (EVMPD). Accordingly, EFPIA requests that** (i) **these data are used populate the list of medicinal products** that have been authorised in the Community. This will save NCAs or MAHs providing these data again and will mean that MAHs will not need to validate the list provided by NCAs. **(ii) the Agency confirms** that the list of medicinal products that have been authorised in the Community in EVMPD and this new list in the database referred to	

	in Regulation 726/2004 will be linked and that MAHs will be asked to validate (or submit) their list only once. **EFPIA does not wish to check duplicatively with respect to both EVMPD and the database referred to under 726/2004.**	
	Interpretation 2: Electronic Submission of Medicinal Product Information (i.e. SmPC etc) EFPIA supports the move to electronic submission of product information (i.e. SmPC, Patient Leaflet, Packaging Text, etc.). The timings proposed in the changes to the Regulation need to be considered separately for the Centralised Procedure and for the other Community procedures and the national procedures. **Centralised Procedure** EFPIA interprets this proposed change in the Regulation to refer to the implementation of electronic submission using the PIM data standards and approach. The proposed timelines in the draft changes to Regulation (i.e. points (a) and (b)) are appropriate for the Centralised Procedure. **Mutual Recognition, Decentralised, National** The PIM electronic submission standards rely on the use of the QRD document templates and standards for Product Information. As the QRD templates and standards are not used fully in the other procedures and are not used consistently by all NCAs for the national procedures, considerably more time would be needed to implement such standards and the associated electronic versions for these other procedures. In view	

	of this, the Regulation should read: *(a) by -/- (six-months after the entry into force of the directive) the Agency shall make public a format for the electronic submission of medicinal product information;* *(b) by -/- (~~eighteen~~ **thirty** months after the entry into force of the directive) marketing authorisation holders shall electronically submit to the Agency medicinal product information compliant with the format referred to in point (a) for all medicinal products authorised or registered in the Community.* Additionally**, in defining these timelines, EFPIA is assuming** that national Product Information will be submitted in the official language of the country in which the product is authorised and that **translation of all Product Information into English will not be required.**	
Page 45 Regulation (EC) No 726/2004 Article 62	With reference to the general comments made on the future role of the new Committee on Pharmacovigilance, on section 3.2.1 and on Article 56(1), we believe that the responsibilities of the CHMP as currently outlined in Article 5 of Regulation (EC) No 726/2004 cannot be devolved to the Committee on Pharmacovigilance. We believe that the CHMP must retain the ultimate responsibility for reaching decisions on matters such as the granting, variation, suspension, revocation etc of marketing authorisations.	