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

COMMENTS FROM JOHNSON AND JOHNSON/ADRIAN THOMAS

COMMENTS ON TEXT

Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
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 (eg, data) from all relevant stakeholders. It would be helpful to clarify how the referral procedures for nationally approved products are to be rationalized. It is important that the Marketing Authorisation Holder (MAH) is given the opportunity to participate, and present their data, in any public hearing.	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, including mandating that the MAH be given the opportunity to participate, and present their data, in the public hearing should one take place.
Page 4 Section 3.2.1 Impact	Reference is made to '…the robustness of pharmacovigilance…' but this is not defined. Not defining robustness of pharmacovigilance and the way in which it is measured may lead to arbitrary decisions and lack of legal certainty. Guidance should be provided on how robustness	Provide a definition for robustness of pharmacovigilance. Provide guidance on how robustness of pharmacovigilance is measured. This guidance should be linked to inspection guidance for clarity.

	of pharmacovigilance is defined and measured.	
Page 5, Section 3.2.2 Impact	'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.	'Clear roles and responsibilities will increase the robustness of pharmacovigilance which will drive innovation by increasing confidence and…'
Page 5 Section 3.2.3 Key changes	The proposal to have a Pharmacovigilance System Master File (PVSMF) maintained on site is welcomed. 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' (DPS) previously submitted to a Competent Authority, for the change from the DPS that is currently required to the PVSMF. It is proposed that a Type I variation or a notification letter be submitted to remove the DPS from the dossier. It has been 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 becomes the supervisory authority for pharmacovigilance. This would appear to be more stable and less subject to change.	Specify the requirements for the PVSM. <u>'In the case of medicinal products authorised -/- [after 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 DPS is replaced by the PVSMF and that the DPS will no longer be kept up to date as part of the said marketing authorisation.'</u> Specify that the Member State in which the legal entity of the MAH resides becomes the supervisory authority for pharmacovigilance.

Page 5 Section 3.2.4 Key changes	It should be clarified what the circumstances are that require submission of a risk management plan. Risk management plans should only be required when needed. For clarification, add 'agreed' to 'Ensure that the key risk management measures are included…' Risk management plans (RMPs) for all biologic medicinal products including innovator and biosimilar products must address known or potential safety concerns. As a result of their limited experience, biosimilar medicinal products should be even more rigorous than those for the reference product as the biosimilar has been approved on a smaller clinical data set than the reference product and the risk associated with these products can only be established in a post-marketing setting. It will help to clarify the role of the RMP in biosimilars. Traceability of biosimilar medicinal products is of great relevance when preparing RMPs. Even though the most robust tools should be used for product identification, including the non-proprietary name, lot numbers, drug codes etc, these data might not always be available and therefore a method of identifying biosimilar products must be adopted. A Europe-wide solution for the identification of products should be an outcome of this process.	Clarify the circumstances that require submission of a risk management plan. 'Ensure that the agreed risk management measures are included…' Specific language requiring the new committee replacing the PhWP to commence a public process involving authorities, manufacturers and interested academics. There should be specific milestones and a date set for a formal recommendation on the establishment of a Europe-wide solution addressing product identification.
Page 6 Section 3.2.4 Why	The legal basis for requesting risk management plans for authorised products…provisions'. The legal provisions should be clarified and included as an article in the amended directives.	Clarify the legal base for requesting risk management plans for authorised products.
Page 6 Section 3.2.4 Impact	'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 impression that MAHs create poor quality risk management	~~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.~~

	plans and have poor compliance. Additionally, the proposals are not anticipated 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.	
Page 6; Section 3.2.5. Key changes	For non-interventional post-authorisation safety studies, the criteria for what constitutes "promotional objectives" and 'light oversight' are not defined. 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 (eg, 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.	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. ' Light oversight (by EMEA pharmacovigilance committee only if study will be conducted ~~to be~~ in more than one Member State and by Member State if study will be conducted in only one Member State) of non-interventional post-authorisation safety studies to ensure that they have health rather than promotional objectives.' Guidance should be provided on how reportable information from promotional programs will be handled.
Page 7 Section 3.2.6. Key changes	It is proposed that the EMEA to take on scanning of scientific literature and entering case reports from the literature on Eudravigilance. The peri and post-marketing publications for innovative products are of direct interest to the MAH in order to perform an adequate benefit-risk assessment. Furthermore, the innovative industry is the party that for many publications definitively can link literature cases with those reported earlier as clinical study case reports. Additionally, other agencies outside the EEA will still mandate expedited reports from the industry on published suspected adverse drug reactions. For newly approved products (since there are many	'…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'

	publications), the proposal puts a significant burden on the EMEA, does not reduce the burden for the industry and increases the potential for double reporting. 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. It should be clarified whether Agency will use the same standards for literature review as detailed in Vol. 9A and whether they will enter the same data into the database as ICSRs. Will the Agency follow up on these reports for more information? Will the EMEA send a note to the authors for more information or will the EMEA ask the MAH to follow up with the author for more information. It is rare that a publication has all the information required to make a full assessment of the case. It should be clarified 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? 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.	Clarify whether the EMEA will use the same standards for literature review as detailed in Vol. 9A and whether they will enter the same data into the database as ICSRs. 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?
Page 7 Section 3.2.6	Mention is made to report of medication errors that result in adverse reactions only.	' Regarding medication errors the definition of adverse drug reaction would be clarified as would the reporting rules to make

Key changes	Medication error 'near misses' where the patient did not receive the product could provide valuable information – especially with regard to cases of name confusion/packaging similarities. These should be reported also – as consistent with Vol. 9A (Cases not associated with adverse reactions and near misses should only be reported in accordance with national requirements.)	clear that medication errors that result in an adverse reaction, and near misses, should be reported to the competent authorities for medicines (and oblige Member States to ensure any Patient Safety authority is also notified).'
Page 7 Section 3.2.6 Key changes	The idea of placing a medicinal product on a list of intensely monitored medicines raises the following issues: 1. It creates a perception in the mind of the prescriber that medications not on the list are safe and thus don't require monitoring, ie, reporting. 2. It stimulates reporting for those drugs on the list, thereby creating a disproportional safety profile for those on the list compared to 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. 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. It should be clarified whether all new products would be placed on the list or whether there will be a risk assessment done before authorisation, which would allow some products to be left off the list (eg, generics) of intensely	A detailed guideline with 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.

	monitored drugs. 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 criteria for removing medicinal products from the list should be specified. It is recommended that all biosimilar medicinal products be automatically added to the list of intensively monitored medicines for a scientifically appropriate period, so that patients, pharmacists, and physicians are aware of the need for enhanced vigilance. A centrally held EU list of intensively monitored medicines should replace national lists of intensive monitored medicines and not be in addition to such lists.	All biosimilar medicinal products be automatically added to the list of intensively monitored medicines for a scientifically appropriate period, so that patients, pharmacists, and physicians are aware of the need for enhanced vigilance. National lists of intensive monitored medicines that add to the EU list of intensively monitored medicines should not be permitted.
Page 7 Section 3.2.6 Key changes	Patient adverse reaction reporting forms should not be part of the patient information leaflet. 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. The increased size of the patient information leaflet may also present manufacturing difficulties as this will make the packaging 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. This could require retooling on the packaging line. This is a significant issue from a resource/cost impact perspective for industry. There is some concern that, by providing Patient adverse reaction reporting forms in this way, HCPs would feel less	• MAHs to provide toll-free company telephone numbers 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

	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 reporting forms are to be included with patient information leaflets, then they should be included with all prescription products. If such forms were to be introduced, would readability testing of the form need to be conducted at the same time as the patient information leaflet? An alternative way to empower patients to report side effects would be to provide toll-free company telephone numbers and company owned/monitored website information. This should be a more efficient and effective way to collect the information as well as to collect any follow up information. This 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 8 Section 3.2.7 Key changes	'Link PSURs to risk management planning and therefore the knowledge about the safety of the product. Where there is no risk management plan provide for periodicity of reporting to be proportional to the knowledge of safety i.e. no PSURs for old established products. Balance this major reduction in routine periodic reporting by making clearer the current requirements on MAHs to report any changes in the benefits and risks of their products and to ensure the product information remains up to date.' It is recommended that PSURs continue for 'old established products' at a reduced periodicity. For older products with	'Where there is no risk management plan provide for periodicity of reporting to be proportional to the knowledge of safety i.e. reduced periodicity of ~~no~~ PSURs for old established products.'

	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. Furthermore, companies would have to prepare them for Heath Authorities outside of the EEA. Also, established products given for new indications/different doses etc (eg, aspirin) need risk/ benefit assessment in any new context. Clear guidance should be provided on the links between risk management planning and the PSUR. A definition of 'old established products' would be helpful.	Provide clear guidance on the links between risk management planning and the PSUR and a definition of 'old established products'.
Page 9 Section 3.2.8 Key changes	All regulators should use the same dictionary (MedDRA) to reduce burden on industry and ensure consistency of AE reporting terminology. Consequently, we do not agree with the suggestion to support development of an EU drug dictionary and recommend modification of ' Ensure that there are clear legal provisions on the provision of medicinal product information by companies including to support the development of an EU drug dictionary ' accordingly. Additionally, we do not expect the cost to industry to be neutral if we have to interact with another database.	Ensure that there are clear legal provisions on the provision of medicinal product information by companies ~~including to support the development of an EU drug dictionary~~.
Page 9 Section 3.2.9 Key changes	The Summary of Product Characteristics and Patient Information Leaflet should be revised, not 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 the safety information that is already contained in existing sections of these documents (e.g. Warnings and Precautions) and thus be confusing. Additionally, doctors and patients are already inundated with the length of information in these documents. It could encourage the reader to focus and rely on the 'key safety	'…with a transitional phase of 5-years (i.e. update the product information at the time of the next renewal or <u>labelling review</u> ~~next major variation~~)' Provide guidance on how this section should be written (ie, level of language).

	information' section for the complete safety information about the product and thus form the basis of prescribing or using the product when this section would only contain some of the essential safety information that is required to appropriately prescribe or use the product. 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 (ie, level of language) and define what comprises key safety information. It is also important to communicate the benefits of a product and, in some cases, the risks of not taking the product. The proposed transitional phase should be at the time of the next renewal or labelling review as not all major variations lead to a change in the labelling.	
Annex 1		
Page 11 Article 1(11)	The definition of adverse drug reaction should be consistent with the ICH definition. More emphasis should be placed on people using drugs 'within the approved label'.	'Adverse reaction: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.'
Page 11 Article 1(13)	A definition of unexpected adverse drug reaction should be retained and be consistent with the ICH definition.	'Unexpected adverse reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product

		information.'
Page 11 Article 1(16)	The definition of abuse should be retained.	'Abuse of medicinal products : Persistent or sporadic, intentional' excessive use of medicinal products which is accompanied by harmful physical or psychological effects.'
Page 12 Article 1(15)	The definition of "Post authorisation safety study" is too broad. Furthermore, it is not clear on which type of study may be post authorisation study but not post authorisation safety study. This leads to ambiguity. A definition for "Post Authorisation study" should be included in the Directive along with guidance to differentiate "Post authorisation safety study" compared to "Post Authorisation study".	Modification of 'Post authorisation safety study: A pharmacoepidemiological study……conducted with the primary aim of identifying, characterising or …..' Proposed definition: 'Post-authorisation study: 'Any study conducted with an authorised medicinal product.' A Post authorisation study can be a clinical trial if it falls under the scope of the Clinical Trial Directive, or a non-interventional study if it falls outside the scope of the Clinical Trial Directive. Depending on the primary aim of the post authorisation study, it may fall into the scope of 'Post authorisation safety study' or 'Non-interventional post authorisation safety study (as defined in Article 101h)'.
Page 12 Article 1(33)	Risk management system A more accurate description of risk management system would be risk management arrangements. This is because a risk management system is part of the PV system but also includes aspects such as special collection of important adverse reactions from the pharmacoepidemiological studies and activities in the market place agreed in the Risk Management Plan (RMP). The wording should be clarified further with use of 'and/or'.	'Risk management system: 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 13 Article 11 (3b)	'……All suspected adverse reactions should be reported'. For clarification, this should be expanded to detail who the report is to.	'…….. All suspected adverse reactions should be reported to the MAH.'

	The transition measures for introduction of new key safety information should be stated. The proposed statement for intensively monitored medicines should be amended to alleviate concerns that there is a particular safety issue with a new product when there may not be one. [Also, see comments under Page 9, Section 3.2.9]	'For authorised products the introduction of the new section on key safety information shall have a transitional phase of 5-years (i.e. update the product information at the time of the next renewal or labelling review).' 'This medicinal product is under intensive monitoring to gather further information on the benefits and risks. All suspected adverse reactions should be reported.'
Page 15 Article 22	The wording of the conditions should be clarified further with the use of 'and/or' and deadlines should be set in agreement with the MAH/applicant. 'The marketing authorisation shall lay down dead-lines for the fulfilment of the conditions where necessary. Continuation of the authorisation shall be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions.' Definitions or criteria are needed to clarify how will it be determined whether deadlines are necessary and how these deadlines will be set? In particular, how will feasibility be taken into account? The intent here is to try to ensure that requests and deadlines are reasonable. It is important that flexibility be permitted to prevent a regulatory trigger being activated where commitments have not been fulfilled due to unforeseen reasons. 'A medicinal product shall be removed from the list …' should be reworded for clarity.	'(a) the requirement to conduct post authorisation safety studies, and/or, (b) adverse reaction recording or reporting that differs from the requirements of Title IX and/or, (c)…'. 'The marketing authorisation shall lay down deadlines in agreement 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.' 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? 'The Agency will remove a medicinal product ~~shall be removed~~ from the list ….'

Page 16-17 Article 23	Timelines for provision Article 23 states that results from clinical trials which might have an influence on the evaluation of the benefits and risks must be sent to the competent authority. Timelines should be provided in relation to when this information must be supplied. Guidance should be provided in relation to Investigator Initiated studies where the MAH will not necessarily know all the clinical trials being undertaken with their products. 'In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk -benefit balance remains favourable.' Further clarification is needed as to what types of data might be required, what the process is by which the competent authority and MAH can discuss and agree what is needed. We support a collaborative approach to monitor the benefits and risks of a product.	Provide timelines for provision of results from clinical trials. Provide guidance in relation to Investigator Initiated studies. Provide clarification on what types of data might be required and what the process is by which the competent authority and MAH can discuss and agree what is needed. It might be helpful to provide examples.
Page 19 Article 54	Remove article 54(o) as detailing the proposed text on the outer packaging can give the false impression to the user that they should not report adverse reactions with other products where this text is not mentioned. Advice on reporting is addressed in the patient information leaflet.	'~~(o) For medicinal products included on the European list of intensively monitored products referred to in Article 101j, the following statement shall be included "All suspected adverse reactions should be reported (see leaflet for details)~~'
Page 19 Article 59	Section (ba): unclear if it is first sub-section of section (b) or that it could be either in section (a) or (b) '…All suspected adverse reactions should be reported'. For clarification, this should be expanded to detail who the report is to. The transition measures for introduction of new key safety information should be stated.	Create a section (c) '…All suspected adverse reactions should be reported to <u>the MAH.</u>' 'For authorised products the introduction of the new section on key safety information shall have a transitional phase of 5-years (i.e. update the product information at the time of the next

	The proposed statement for intensively monitored medicines should be amended to alleviate concerns that there is a particular safety issue with a new product when there may not be one. [Also, see comments under Page 9, Section 3.2.9]	renewal or labelling review).' 'This medicinal product is under intensive monitoring to gather further information on the benefits and risks. All suspected adverse reactions should be reported.'
Page 20 Article 101a	'…. the 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.' Under current legislation, it is difficult to see how a Member State can ensure that an adverse reaction report associated with a biological medicinal product is identifiable where biosimilar medicinal products are available. 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 foresee how it could be possible to link incidence of events with a particular source or presentation of a biological medicinal product. To be able to uniquely identify and trace a biological medicinal product is critical for two key reasons: 1) to avoid confounding the post-marketing surveillance and risk management activities required in order to identify any rare immunological side effects, and 2) to be able to quickly identify a specific product associated with any quality issues or adverse events. To enable identification, distinct and unique International Non-proprietary Names (INNs) for biosimilars should be adopted and this should be mandated in the legislation. The allocation of a unique INN would enable MAHs to link rare	Revise the legislation to require that: • a distinct INN be assigned to each biosimilar medicinal product from a different manufacturer and • it is not permissible to substitute with a biosimilar medicinal product without a physician's agreement • all biosimilar medicinal products be automatically added to the list of intensively monitored medicines for a scientifically appropriate period.

	but serious side effects with the correct product, minimize risk to patients and enable the MAH to responsibly monitor and manage safety issues associated with their product. 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. A unique INN would also facilitate effective communication and exchange of information among health professionals. Giving a biosimilar medicinal product the same INN as the innovative product will make tracing adverse reactions more difficult and can 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 and • it is not permissible to substitute with a biosimilar medicinal product without a physician's agreement Additionally, it is recommended that all biosimilar medicinal products be automatically added to the list of intensively monitored medicines for a scientifically appropriate period, so that patients, pharmacists, and physicians are aware of the need for enhanced vigilance.	
Page 20 Article 101(b)	Under this Article, the wordings suggest that "Good Vigilance Practice" would be written as a "guideline". However, under section 3.2.2 (Key changes), it suggests that the Commission wishes to adopt a regulation for "Good Vigilance Practice" via comitology. We suggest that "Good Vigilance Practice" should be a Regulation to ensure legal certainty and facilitate public health protection. However, it is important that such a regulation shall replace current directives and guidance, rather than adding to them, so as not to overburden both Industry and competent authorities with additional	'Following consultation with the Agency, Member States and 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:'

	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 'Good Vigilance Practice regulation' would add value rather than just burden, and how patients would benefit or be protected (more than through existing regulations, directives and guidance).	
Page 22 Article 101 d (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 Authority, as appropriate. Common and consistent methodology for monitoring the data in Eudravigilance should be adopted and shared. Finally, MAHs should be able to access data for their products from Eudravigilance.	'2. 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 the marketing authorisation holder, the Member States and the Commission of these findings. The Rapporteur, Reference Member State and National Authority will remain the supervising authority for pharmacovigilance, as appropriate.' Common and consistent methodology for monitoring the data in Eudravigilance should be adopted and shared. MAHs should be given access to data for their products in Eudravigilance.
Page 22 Article 101d (3)	The proposal to provide public access to individual adverse reaction reports may lead to misinterpretation. Individual reports do not provide a full picture of the safety of the product. This provision should be deleted.	'~~3. Individual adverse reaction 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 unless this would compromise the anonymity of the subjects of the reports.~~'
Page 22 Article 101e(1)	It should be clarified whether this section applies to clinical trial AE reports.	'Spontaneous adverse reactions recorded….'

	'Adverse reactions recorded shall be reports where … a causal relationship is a least a reasonable possibility' implies that even for spontaneously reported events the company causality could be determined as 'doubtfully related and such a case will not be recorded. Unless this is clarified, there might be inconsistency in reporting among MAHs. A detailed guidance on what criteria to use for causality assessment must be provided, particularly with regard to reports with very scant information, such as when temporal relationship is unknown. [See also comments to Page 11 Articles 1(11), 1(13) on using the ICH definition.]	Provide detailed guidance on what criteria to use for causality assessment, particularly with regard to reports with very scant information, such as when temporal relationship is unknown.
Page 23 Article 101e(2)	The proposed requirement that all adverse reactions (serious and non-serious) occurring within the EU be reported within 15 calendar days represents a major change in reporting obligations and is unworkable as it is proposed. EU law, consistent with the law in other jurisdictions, should distinguish between serious and non-serious adverse reactions. Special attention, including expedited reporting and follow-up, is appropriate for serious reactions, but attempting to give the same priority to non-serious reactions will overburden the system and divert attention and resources from more significant events. We propose that, routinely, non-serious adverse reactions should instead be reported at periodic intervals, on an aggregate basis as occurs today in the submissions such as the PSUR. There are two situations where 15 day reporting of all adverse reactions may contribute positively to the public health, and these should be most appropriately defined within product-specific risk management plans. Firstly, where there is a need to monitor adverse reactions as part of an identified, or suspected, safety signal at any time during the product lifecycle where expedited reporting of non-	' 2. Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15 calendar days following the receipt of the report, all serious adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community. Non-serious adverse reactions occurring within the EU should only be reported in an expedited manner on request and otherwise in accordance with Vol. 9A Chapter I.6 on Periodic Safety Update Reports.'

	serious reaction will benefit the public health. Secondly where a product may be approved at an earlier stage of development and as part of a conditional approval whereby in consultation with the MAH additional safety information is required to be collected to complete the product profile. It should be noted that these should be considered exceptions and be product-specific.	
Page 23 Article 101e(3)	As Member States receive adverse reactions reported to them by HCP, Member States need to report these to MAHs to enable MAHs to comply with their international reporting requirement.	'Member States shall submit electronically to Eudravigilance and to the MAHs all of these reports within 15-calendar days following the receipt of the report…'
Page 23 Article 101e(5)	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. It should be clarified 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? [See also comments to Section 3.2.6.]	'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. For the purposes of monitoring the literature, a medicinal product will be considered to be 'off-patent' when it first becomes off patent in an EEA country. It shall publish the list of publications subject to this monitoring, and it shall enter into Eudravigilance relevant information from the identified literature.' It should be clarified 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?
Page 24 Article 101f(2)	'Reports should be submitted electronically - Guidance on format should be provided for electronic submission of PSURs where the MAA submission was not in eCTD format. No paper copy should be required in the event of electronic submission.	Provide guidance on format for electronic submission of PSURs where the MAA submission was not in eCTD format.
Page 25 Article 101f (4h)	Assessment conclusions to be made public. The MAH can respond to assessment reports and the ultimate outcome may be different from what was set forth in the assessment report. For example, the assessment report could suggest a	'(h) 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 10 1i.'

	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 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 after MAH response is received and taken into consideration is made public.	
Page 26 Article 101 (h)	The proposal to codify the conduct of non-interventional post authorisation safety study is welcomed. However, since the term is not defined in the Directive, this leads to ambiguity. It is proposed that the definition based on 'Non-interventional' in the Clinical Trial Directive is used.	*Proposed definition:* "*Non -interventional Post authorisation safety study"* 'Non-interventional post authorisation safety study: a post authorisation safety study conducted with the primary aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product 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.'
Page 26 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 appeal procedure should be available in the cases of objection.	Provide details of an appeal procedure for cases where a letter of objection is issued.
Page 27 Article 101h (1e)	'The competent authority or the Committee, as appropriate, may give a recommendation on the submitted protocol within 60 -days.' should be reworded for clarity.	'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 ~~within 60 -days~~.'

Page 27 Article 101h (1f)	Note that any amendments need only be notified to the CA or the committee. It is unclear whether it is intentional that an approval or a letter of no objection is not required and that the change can be implemented immediately. This should be clarified. We support a notification only process with immediate implementation of the change.	Clarify that a notification only process is required with immediate implementation of the change.
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 within 12 months of last patient last visit consistent with the Clinical trials Directive.	'h) T~~he 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 within 12 months of last patient last visit.'
Page 27 Article 101h (1k)	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. [See also comments to Page 25, Article 101f (4h)]	'k) Based on the results of studies the Committee may make recommendations for the product information and these shall be made public after the changes are final via the Agency web-portal.'
Page 29 Article 101k (1-12)	The interaction with the MAH, particularly obtaining input from the MAH, should be delineated. An appeals process should be defined so the MAH can provide its position to an impartial group.	Specify in the legislation the involvement of the MAH. Provide an appeals process.
Page 28 Article 101i (1d)	It is important that the MAH should be given the opportunity to redact confidential information from the Risk Management Plan before it is made public. It would be preferable for only a summary of the Risk Management Plan to be made public for ease of understanding and interpretation.	Include wording providing MAH the right to redact confidential information. '(d) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with Regulation (EC) No 726/2004. Confidential information will be deleted from the plan before it is made publicly available.'
Page 28 Article 101i (1f)	MAHs have the obligation to notify the competent authority of their QPs. The benefit of making the list of QPs public is unclear and appears disproportionate. We believe this is an	~~(f) A list of marketing authorisation holder qualified persons for pharmacovigilance and the Member State in which they reside.~~

	invasion of their privacy and also may increase risk to their personal safety with regards to possible activist activities and, consequently, this should be deleted.	
Page 28 Article 101i (3)	Quote: "… to make a public announcement relating to important information on pharmacovigilance concerns including product withdrawals and major restrictions to the use of a product …" For clarity, reword to reflect withdrawals due to safety concerns as some products are withdrawn for economic reasons.	'3. As soon as the holder of a marketing authorisation has the intention to make 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 29 Article 101k (1e)	A legal basis should be created for the adoption of interpretative guidelines on the concept of 'serious deficiencies'.	'The Commission shall, in consultation with the Agency, Member States and interested parties, draw up detailed guidance regarding the concept of serious deficiencies.'
Page 29 Article 101k	Clarification should be provided for medicines authorised in one Member State only, including clarification of roles and responsibilities for: •Decision making process at the local HA •Industry involvement and consultation procedure before the final decision is taken and communicated COMMUNICATION via the local HA websites: Establishment of a standard template for the communication to public of the products safety information. MAH's websites to refer the same information.	Provide clarification for procedures for medicines authorised in one Member State only.
Page 33 Article 101l (4f)	Audit reports should not be included in the pharmacovigilance system master file and this obligation should be deleted from draft legislation.	'f) Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices ~~and place a report of the audit on the pharmacovigilance system master file~~.'
Page 33 Article 101m	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 (naming, in particular) are not in contradiction inside and outside the EU.	

	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 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 not currently addressed in the proposals. [Also, see comments under Page 20 Article 101a'.]	
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 39 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.	'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 39 Article 117	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.	'1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that: (a) the medicinal product is harmful under normal conditions of use; or ~~(b) it lacks therapeutic efficacy; or~~ (b) the risk-benefit balance is not favourable under the authorised conditions of use; or…'
Page 42 Article 18 (3)	It has been 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 becomes the supervisory authority for pharmacovigilance. This would appear to be more stable and less subject to change.	Specify that the Member State in which the legal entity of the MAH resides becomes the supervisory authority for pharmacovigilance.
Page 43 Article 57(2)	A staggered implementation timeline maybe more feasible depending on date of original approval or the intensive monitoring status of the product. Also, the Agency should provide the product information for centrally approved products since it is already on the EMEA website. It would be helpful to define either here or in a guidance document the expectations regarding updating the database as variations or other updates are approved.	'(b) by -/- (eighteen 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. Medicinal product information will not be required to be submitted for products approved centrally.' Provide guidance on the expectations regarding updating the

		database as variations or other updates are approved.
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.	Define the role, responsibilities and scope of authority of the Pharmacovigilance Committee and it's interaction with the Committee on Human Medicinal Products.

Please feel free to add more rows if needed.