Comments on: Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance: Public Consultation on Legislative Proposals

COMMENTS FROM: Pharmaceutical Research and Manufacturers of America (PhRMA)

950 F Street, NW, Suite 300

Washington, DC 20004 USA

Contact Person: Alan Goldhammer, PhD; Phone: 202-835-3533; e-mail: agoldhammer@phrma.org

GENERAL COMMENTS

The stated goal of this proposed legislation is to strengthen the EU pharmacovigilance system for human medicines. Conceptually, PhRMA member companies support this goal, and believe that the proposed legislation, if enacted, would lead to greater patient safety in the European Union. The proposed legislation contains a number of excellent suggestions, such as simplification of existing requirements for a detailed description of the pharmacovigilance system, which may help improve safety of use of medicines and decrease the administrative burden for national competent authorities, EMEA and the pharmaceutical industry. In addition, centralized, rapid decision-making on safety issues should benefit patients and improve efficiency.

However, sensitivity to certain aspects of national sovereignty and general legislation should be carefully considered when revising these proposals for a strengthened EU pharmacovigilance system. For instance, under the delegation of tasks among Member States (MS) described in Article 101l(2), it is not clear whether delegation of tasks extends to delegation of decisions on penalties, such that an MS could levy a penalty on an MAH that is a legal entity in another MS. In addition, we are concerned that the proposed legislation could (a) provide a framework for a prescriptive pharmacovigilance system that seems to minimize the possibilities for valuable dialogue and discussion among important stakeholders, particularly MSs and MAHs; and (b) create the potential for increasing global disharmony in pharmacovigilance activities. Both of these latter two points could have adverse impact on public health in the EU. In addition, it will be important to ensure consistent implementation across all member states since there apparently will not to be a single Council Regulation on Pharmacovigilance to make the new legislation legally binding and not open to interpretation by the various Member States.

In the interest of further simplification, we raise the question of whether there is a need for both a Directive and a Regulation. Since 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, the Agency, and Member States to proceed with greater clarity, save time and deploy resources in a more efficient manner.

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A number of the proposals (such as highlighting "key safety information" in the SPC and Patient Information Leaflet; publicly posting Risk Management Plans; expanding the assessment reports of the Competent Authorities to cover Risk Management Plans; public listing of products subject to "intensive monitoring"; public availability of individual AE reports, etc.), if implemented as written, without appropriately worded caveats or limitations, are likely to have unintended negative consequences. While we live in a world with increasing expectations about transparency and access to information, the situation remains that many members of the general public are unlikely to be able to put the information that will be made available into proper context. The end result may be to create undue alarm and an unwillingness to continue taking certain key medicines or to discontinue vaccinating with key vaccines based on misunderstanding of the information available. The availability of the information also is likely to create additional liability exposure for MAHs -- perhaps outside the EU -- as the documentation posted by the Commission will be scrutinized by plaintiffs' lawyers looking to use the fact that a drug as been placed on the list of "intensively monitored drugs" as evidence that it must be unsafe, or looking to take issue with different approaches used by authorities in the EU and elsewhere. While these risks are inevitable, the issuance of carefully worded guidance or other "companion" documents to the legislation can help to mitigate them.
While the effort to focus on less administrative burden is clear for many of the suggestions, the proposal to submit non-serious reactions occurring in the Community within 15 days may have significant negative impact and severe resource implications for companies, especially ones that must meet global obligations. We question the public health benefit of this requirement.
Establishing and maintaining a European list of medicines under intensive monitoring needs more definition and clarity to ensure the proper outcome. The process for selecting drugs to be placed on this list must be transparent, well defined, and managed impartially. Otherwise, there is a risk of this measure being unintentionally punitive to the companies with more advanced, comprehensive and proactive surveillance systems.
Audit reports should not be included in the PV Master file and this obligation should be deleted from draft legislation.
Literature searches by EMEA will not result in any cost savings for industry, while increasing costs for the EMEA, since companies must conduct literature searches to meet global obligations and for risk assessment. Furthermore, this may result in duplicate cases being included in the EU database. Since the proposed EMEA literature search will provide no resource savings for either EMEA or industry for newly approved products, the most cost-effective allocation of EMEA resources for this activity should be to mature, off-patent products.
Encouraging direct patient reporting as planned in the draft legislation, for example by proposing to include AE Reporting forms in Patient Information Leaflets, could negatively impact HCP reporting and result in poorer quality reports for companies and regulators.
The new proposed EU Drug Dictionary would be a real negative for industry in terms of costs/resources to maintain in addition to non EU HA dictionary. Any EU Drug Dictionary should be consistent with international standards currently under development (ICH M5).
International harmonization should be the goal of any new or revised legislation. Unfortunately, the proposal introduces several concepts that are not consistent with accepted ICH guidelines, for example, a revised definition of adverse reaction, and expedited reporting for submitting non-serious ADR reports. ICH definitions and guidelines should be used to ensure global consistency and optimize the efficient use of heath authority and industry resources.
Importantly, the overall plan needs more careful consideration for biologics than the draft provides. Multiple similar biological medicinal products (biosimilars) with the same INNs but different clinical profiles are now on the market and that this situation is likely to become more complicated.

In general, the majority of changes proposed within this draft legislation are well thought through and very much welcomed. The comments below focus on our major areas of concern, particularly items of significant practical/logistical impact, areas where compliance questions arise, and areas for which clarification is requested.

SPECIFIC COMMENTS ON TEXT

Page + section + paragraph	Comment and Rationale	Proposed change (if applicable)
3.2.1 page 3 and Article 101k(9) (page 30)	With regard to establishing a committee with clear responsibility for coordinating pharmacovigilance, and rationalizing referral procedures: We are supportive of a stronger legal mandate for 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) (page 43) states the new Committee on 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? We agree strongly that, at present, evidence-based conclusions about real safety issues and their mitigation are not comprehensively implemented across Member States; 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 formal 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 (e.g., data) from all relevant stakeholders. To ensure a robust system, further definition of the proposed role and scope of the envisioned Pharmacovigilance Committee,	Clarify the practical aspects of the new Committee, i.e. • What will be the decision making process and will such decisions no longer need to be ratified by the CHMP? • What will fall within the scope of this new Committee? e.g., RMP reviews signal detection, risk-benefit analysis etc. Proposed revision to Article 101k, number 9: "9. 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, the legislation should describe details of the role and interactions of the proposed Committee and ensure public consultation prior to implementation.

	including interaction of the Committee with the CHMP and Member States, should be subjected to public consultation prior to implementation.	
3.2.1 page 3/4 and Article 101k Page 29/30	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 terms “light oversight” and “light procedures” are very vague, and the process around a public hearing is not fully defined.	Further clarification is requested from the Commission with respect to the intent/definition of the terms “light oversight” and “light procedures”. Further clarification is also requested on what the triggers are for a public hearing; are they restricted to those mentioned in Chapter 6, Article 101k, 1; a to e? (Page 29) and does this article apply only to national and Mutual recognition or also Central products? Chapter 6, Article 101k, 6; states the agency shall publicly announce a public hearing within two working days via the web portal. In this respect we suggest notification to the MAH in advance of release via the web site to the public.
3.2.2 page 4	Noting that a further Regulation on Good Vigilance Practices (GVP) will follow, GVP should be aligned with international standards per ICH E2D. Will this be the case?	Clarify that the proposed Regulation on Good Vigilance Practices will be aligned with ICH E2D.
3.2.3 page 5 also Article 101l(2), page 32, and Regulation (EC)726/2004, article 18(3), page 42/43	PhRMA companies fully support the concept of a simplified detailed description of the PV system and the concept of submitting the PV system master file on request or reviewed at inspection. We do not agree that the specific supervisory authority for PV for centrally authorized products should be the member state where the QPPV resides. The supervisory authority should be tied to the system, not to an individual, recognizing that the electronic age enables “residence” criteria to be flexible for individuals. The provision as it currently stands could present issues for industry when hiring QPPVs, particularly for small MAHs who outsource the QPPV role as they would need to insist that the QPPV be located at one EU country for inspection reasons. Tying inspections to the QPPV location may also exclude people from becoming QPPVs when residing in the smaller/newer member states.	The specific supervisory authority for PV should not be tied to the residence of the QPPV but should instead be assigned to a member state that the MAH designates as the most appropriate to support scrutiny of the PV system. This would normally be “head office” state for EEA-based companies, or may be the member state where the PV master file and system is housed/accessible in the EEA for MAHs with their HQ located outside the EEA, and/or where PV functions are split between different locations.

3.2.4 pages 5/6 also Article 8(3)(1aa), page 12 and Article 101p, page 34	We agree with the position that risk management plans (in addition to the SmPC) should be required only when they are needed. The proposed language in Article IX referring to risk management plans should be strengthened and consolidated to clarify the proposal. Clear examples should be provided of when risk management plans are "needed" otherwise the authorization process may be delayed. We suggest that special attention be paid to Risk Management Plans for biosimilar medicinal products because these products may have been approved on reduced data sets compared to the reference product and will carry different risks from the reference product, which risk should be evaluated once these products are on the market. Care must be given to the interpretation of "compliance" with RMP commitments, as in some cases every effort can be made to conduct a safety study but circumstances unforeseen by the MAH or authorities, such as insufficient uptake of the product following approval, may make it impossible, for instance, to recruit within agreed timelines. In such circumstances, there should be explicit leeway for the authority and MAH to modify or amend the RMP. With regard to the statement in the “Impact” paragraph on page 6, “…ensuring that high quality, EU safety studies are done…”, 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 dependent on local medical practice.	In Directive 2001/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 that conveys unequivocally the intent of Section 3.2.4, such as: *“Risk management plans are submitted only when they are needed.”* Introduce text to indicate that 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. Companies should be deemed in compliance if they can prove that all reasonable efforts were made to fulfil the RMP obligations. Please clarify the intent of this statement.
3.2.5 page 6	We welcome efforts to harmonize national legislation in regard to Post Authorization Safety Studies but there does need to be more clarity around the definition of PASS studies in line with the	We propose that consideration be given to the contents of the EFPIA 2007 position paper on PAS/PASS.

also Article 101g/h, pages 26/27	EFPIA PASS position paper. In addition, what does "light oversight" mean in this section, and what is the value added if protocols are reviewed and progress reports are written? Also, the criteria for what constitutes "promotional objectives" are not defined. The requirement for review and approval of protocols for all non-interventional PASS outlined in Article 101h creates some issues when PASS are requested and agreed by other regulatory authorities (e.g., FDA) as a condition of approval, and will include centers within the EEA. We have practical concerns about PASS studies requested by agents other than the CAs, such as pricing authorities, or conducted by external agents such as physicians and academic institutions. Industry is usually obligated to provide some support/sponsorship to such studies but often has little control or access to data to enable the new provisions around such studies outlined in Article 101h to be adhered to. See also separate comments on the definition of Post Authorization Safety Studies (Article 1(15)), below.	Wording should be added to clarify the scope and meaning of "light oversight" by EMEA and how this "light oversight" would be coordinated with the Rapporteur/Reference Member State. Also define "promotional objectives". Consider excluding those studies which have been required by another agency from the requirement to have protocols reviewed and approved. With respect to PASS studies requested by agents other than the CAs, we request that such circumstances are acknowledged in the legislation, as currently only one source of initiation/ conduct of such studies is recognized, i.e. the MAH.
3.2.6 page 7 also Articles 101d and 101e, pages 22/23	*1. Reporting to Eudravigilance* Provisions strengthening the role of EudraVigilance as a single, centralized pharmacovigilance database for the EEA are much needed and welcome. We welcome the proposal that all serious 3rd country reports are submitted to Eudravigilance only, noting that it is essential that individual MS CAs will commit to removing any local requirement to also submit directly to them as this would defeat the objective of the proposal. All case reports submitted 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 analyze aggregate data. 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 be required within 15 days	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. Suggest that, all reports not being equal, timeframes for reporting continue to reflect the seriousness of the ICSR in question.

	(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 prioritizing workload, plus presumably Agencies will need to provide industry with both SAES and NSAES sent directly to them within the same timeframes.	
	2. Literature It is anticipated that pharmaceutical innovators, particularly those companies with global operations, will continue to scan and report safety information from the published literature to remain in compliance with requirements outside the EU and to perform adequate benefit-risk assessments. Further, for many publications, the innovative industry is the party that can definitively link literature cases with those reported earlier as clinical study case reports. For newly approved products, the proposal puts a significant burden on the EMEA, does not reduce the burden for the industry and increases the potential for double reporting. The proposed legislation does not indicate whether EMEA will report the information gleaned from the literature to MAHs, or who would have responsibility for carrying out searches on local literature and on non-English language literature.	We suggest that the Commission adopt one of the following approaches: • Limit the proposal for EMEA to scan and data enter case reports from the worldwide published literature to mature, off-patent products. • Specify that EMEA will conduct reviews of the worldwide scientific literature and report literature information to MAHs (including format and timing of such reports).
	3. Medication errors Additional clarification regarding reporting of medication errors is needed. Mention is made only of medication errors that result in adverse reactions. In addition, the language on page 7 indicates that medication error reports should be submitted to the Competent Authorities, and that CAs should ensure that any Patient Safety Authority is also notified. Please clarify that medication error reports should be submitted to EudraVigilance as any other adverse reaction report, and define “Patient Safety Authority”. In addition, medication errors reported directly EudraVigliance or CAs should be communicated to MAHs.	The proposed legislation should specify how medication error reports are to be handled. It should also clarify that medication error reports should be submitted to EudraVigilance as any other adverse reaction report, and define “Patient Safety Authority”. Primary responsibility for recognizing and reporting medication errors that result in adverse reactions lies with the healthcare delivery system, e.g., physicians, pharmacists, nurses, et al., and not with MAHs. MAHs would report medication errors of which they become aware, but an active surveillance system and “policing” would not be an MAH responsibility. 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 etc. These should be collected also – as consistent with Vol. 9A.
	4. Medicines under intensive monitoring The concept of a list of intensely monitored drugs raises the following issues: • It creates a perception in the mind of the prescriber that medications not on the list are safe and thus don't require monitoring, i.e. reporting. • It stimulates reporting for those drugs on the list, thereby creating a disproportionate safety profile for those on the list compared to others in the same therapeutic class not on the list. • 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. 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 criteria for inclusion on the list of intensely monitored products, it may place such companies at a competitive disadvantage. The process by which the public list is established and maintained should be described, and should be subjected to public consultation prior to implementation. (Also see 101j, p 29). Would the envisioned public list of intensively monitored products be those that have a formal Risk Management Plan in addition to the SmPC and routine pharmacovigilance specification? Clarification is also needed regarding products which are not under intensive monitoring because they are new, but because a safety signal is being investigated. Would those products need to be reclassified as medicines under intensive	The proposed legislation should specify how the public list of medicines subject to intensive monitoring would be established and maintained, and that the list of products under intensive monitoring should be maintained at the EU rather than the MS level. It is imperative that the proposed process be subject to a public consultation period. The proposed legislation, or a future detailed guideline, should specify 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. For example, 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. If all newly approved products are automatically included in the list, it might be better to state, "Because this is a newly approved product, it is under Intensive Monitoring" to alleviate concerns that there is a particular safety issue with a new product when there may not be one.

	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, in addition to the EU list of compounds under intensive monitoring, their own country lists of additional compounds under intensive monitoring, as is the case at present. *5. Adverse reaction reporting forms* We do not agree that each pack should contain an adverse reaction reporting form, as this will make current packs much bigger and interfere with manufacturing operations, particularly given multiple language requirements within the EEA. In addition, in most cases, the AE forms are likely to be discarded by patients at the time the package was opened, causing unnecessary monetary and paper waste. Also, by doing this, HCPs would feel less obligated to report potentially significant SAEs since the mechanism was being provided to consumers. In order to "empower patients to report side effects," we suggest providing toll free company telephone numbers and company owned/monitored website information. This is also less costly and time consuming for the patient. Consideration needs to be given to additional implications involved with the increase in consumer reports, including: • Maintaining the quality of spontaneous ADR reports amid 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 reports in all languages? • Who will perform the translations? • Does this request impact PSURS for medicines under	In order to "empower patients to report side effects," we suggest providing toll free company telephone numbers and company owned/monitored website information. This is also less costly and time consuming for the patient. Provide clarification regarding the implications of increased consumer reporting. We suggest that consumers be able report all AEs to either the MAH or the national authority, with MAH and CA having access to the data in Eudravigilance.

	intensive monitoring? 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. It may be confusing for patients to be asked to report to the MAH for intensively monitored drugs and to the national authority for all other drugs. We suggest that both reporting routes should be acceptable with MAH and CA having access to the data in Eudravigilance.	
3.2.7 page 8 also Article 101f, pages 24/25	While we support the suggestion to link PSURs to risk management planning and therefore to knowledge about the safety of the product, this document provides no guidance on the issue. We would like to see language that clearly spells out content of the PSUR and the RMP and details on when and how they are needed and linked to each other and also when one is needed and the other not. 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. Although discontinuation of PSURs for old products would reduce workload, there would need to be consideration of matters such as when they may need be re-initiated, a definition of what constitutes an "old product", the label change process in their absence, etc. With regard to the reference dates for PSURs, the Committee should leverage on the Head of Agencies initiative and the deriving list of reference dates, as agreed between the national authorities and the MAHs and published on the HoAs web site. Starting a new initiative with an independent harmonization effort would be a duplication/repetition of work and by changing what was agreed so recently would create unnecessary confusion.	Provide clear guidance on the links between the RMP and the PSUR. Revise the derogation for requiring PSURs so that it is independent of the legal basis of the registration application, so that innovator products that are available as generics (i.e., “old established products”) do not require PSURs. Consider introducing the original concept of a very much “simplified” PSUR for older products combined with continued use of the recently introduced EU work-share process. Suggested revision: “*…the committee to: reference the public list of reference dates for drug substances for the reporting cycle, as agreed between the national authorities and the MAHs and published on the Heads of Agencies website; requests for changes…”*
3.2.8	We welcome the increased coordination of the provision of	Suggest adding that there is one single contact point identified

page 9 also Article 101i, pages 27-29 and Article 101k, pages 29-31	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. It is important to avoid contradictory and inconsistent messages on the same safety issue; therefore, we endorse the concept that a single agency, EMEA, would issue safety communications. We endorse the concept of a single point of entry to public websites of the competent authorities. However, safety information available on the web portal should be accompanied by educational material, and presented in context with benefit information. How will the EMEA ensure standards with 27 MS websites? 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. Ex-EU pharmacovigilance information, taken together with EU-sourced information, may benefit the public health. 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. The EU drug dictionary should drive to international standards currently under development.	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. 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 prospective stakeholder consultation Add reference to the International Standard under development (ICH M5).
3.2.9 page 9	The section on key safety information should include more detail, including a definition of “key safety information”. Section 3 of the SmPC seems to be a strange location for key safety information. This section comes before the actual indication and it would give a wrong perception of the product. Benefits of the product should also be considered, not only risks. Results of large outcomes trials confirming providing further benefits to patients should be included in the indication section. The documents should be revised, not added to, so that safety information is presented in a clear and understandable manner. Doctors and patients are already inundated with the length of	The changes to legislation should also describe how this section should be written (i.e., level of language) so that this section is geared for consumer/lay reader. We would like to have a better understanding of the content of the new key safety section to be in a position to judge if this section provides added value or if another existing section could be revised to meet the needs. Suggest review of what is being done in US. Is this a transatlantic simplification opportunity? The documents should be revised, not added to, so that safety

	information in these documents. It is already overwhelming and hard to readily find information. The idea of enhanced selective warnings in SmPCs (e.g., a modified "black box" section) may be beneficial to patients. However, practical issues arise in implementing this. Considerations regarding the presentation of safety information in the SmPC and Patient Information Leaflets include: • There is no assessment tool for selecting what are "key messages" or "most important safety information". These are undefined in current regulatory documents, and 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 that patients need. • It could also have the effect of "steering" certain patients toward or away from alternative therapies. • If this new section grows to be a substantial sized section, then it will compete with other information in the SmPC, and this could cause confusion or result in patients and prescribers overlooking truly essential information. • As a general principle, for the SmPC to be an effective reference document, it is best to present safety information in a single location so that users do not need to look in two separate places. Before undertaking the proposed change, market research or other studies should be conducted to assess whether placing selected information in a separate section of the SmPC (a) makes it more likely to be read, (b) does not make other information <u>less</u> likely to be read, and (c) enhances patient safety. Evidence that there is a protective effect on patients is currently lacking. The strategy behind providing selected information in this way might best be targeted at protecting at-	information is presented in a clear and understandable manner. The revision should include reducing the length and volume of information and making the safety information a unique font at the beginning so it is easily seen and understood. This is particularly important for the Patient Information Leaflet. Before undertaking the proposed change, market research or other studies should be conducted to assess whether placing selected information in a separate section of the SmPC (a) makes it more likely to be read, (b) does not make other information <u>less</u> likely to be read, and (c) enhances patient safety.

	risk patients, not a general reduction in drug use: the former is in the public health interest, the latter is not. It is possible that proponents envisage the SmPC as a warning document rather than a reference document, and it may be difficult for it to be both.	
	Directive 2001/83/EC	
Page 11	Several definitions are indicated as being eliminated. We question the rationale for this, as common definitions are usually helpful in preventing different interpretations.	
Article 1(11) Page 11	The adverse event definition is not that of ICH, it would make sense to have the same definition globally. The revised definition appears to eliminate consideration of “in” and “out of label” use and we are unclear as to why this would be appropriate. Shouldn’t more emphasis be placed on people using drugs “within the approved label,” in terms of dosage/frequency especially?	Use ICH definition. If this definition is no longer appropriate, a revised consensus definition should be developed via ICH.
Article 1(13) Page 11	We do not understand the rationale for deleting the definition of unexpected ADR. Although this may not affect expedited single case reporting of post-marketed cases, the expectedness information is considered important within pharmacovigilance to detect new risks not covered in safety reference documents. In addition, we note that the term “unexpected” still appears in Article 101a (page 20).	Use ICH definition. If this definition is no longer appropriate, a revised consensus definition should be developed via ICH.
Article 1(16) Page 11	It is not clear why the definition of abuse is being eliminated. A new definition of abuse, clearly differentiating abuse from misuse and from dependence and taking into account the positioning of drug abuse in MedDRA, would be welcome. This should be agreed in a global consensus forum, e.g., ICH, CIOMS.	
Article 1(15) Page 12	The PASS definition should be strengthened to differentiate PASS from other studies. The proposed legislative change would extend the definition of PASS to any study conducted post-authorization, including those to explore the drug in new indications or new patient	The definition should be revised to specify "clinical study" rather than "clinical trial." More importantly, wording should be revised to clarify that PASS should include studies conducted under a risk management plan, but should not include studies conducted for further development. “Post-Authorisation” should refer to the existing authorization (i.e., keep the wording “in accord with the

	populations, i.e., during further development activities. This would create overlap and conflicting and/or multiple duplicative requirements. Separating the two situations, (1) PASS, whether studies within label or within the boundaries of a risk management plan, and (2) trials conducted to further product development, would help to simplify and clarify the requirements. We recognize that studies conducted under a risk management plan may include situations not previously studied and, therefore, not strictly within the label. However, studies conducted as part of a risk management plan are considered PASS.	marketing authorisation" in the definition). Consideration should be given to explicitly including in the definition that a PASS is primarily conducted to address a specific safety concern and/or with safety as the main objective. In addition, consideration should also be given to including that a study may also qualify as a PASS where the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s). In practical terms, this may be set as an arbitrary size (i.e. 1000 or more patients receiving the authorised product).
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 QPPV should not be held accountable to a standard or requirement that is not and can not be clearly defined.	Amend this article as follows: "…*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*".
Article 8(3)(iaa) Page 12/13	"This risk management system shall be proportionate to the identified **and** potential risks taking into consideration the information available on the medicinal product." Suggestion – delete highlighted word "and" – all risks are potential and only those that are knowable can be incorporated into a risk management plan. Possible alternatives: "…identified and scientifically-plausible potential risks…" or "…known and identified potential risks…" The document does not indicate which body will assess the adequacy of proportionality. What measures will be adopted to guarantee an adequate level of consistency across evaluators?	Suggested revision: "…proportionate to the identified potential risks…."
Article 11(3b) Page 13	As noted above, a definition and guidance regarding "key safety information" is needed.	Add a definition and guidance.
Article 22 (1) Page 15	"*The marketing authorisation shall lay down dead-lines for the fulfilment of the conditions where necessary. Continuation of the*	Definitions or criteria are needed.

	authorisation shall be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions." The wording is a bit vague. How will it be determined whether deadlines are necessary? How are these deadlines set? In particular, how is feasibility taken into account? The intent here is not to look for excuses not to complete a study, but to try to ensure that requests and deadlines are "reasonable."	
Article 23 Pages 16/17	In the fourth paragraph, the reference to results of clinical trials should clearly specify that this refers to company-sponsored clinical trials. *"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."* In addition, the breadth of the requirement for the MAH to keep product information up to date needs to be clarified, so that sensible labelling practices can prevail. Who determines that the benefit-risk balance remains positive? If the company, must the agency agree? Must this agreement by the agency be documented? Suggest revising to say the "benefit-risk balance remains acceptable"? Does this need to be more specific, e.g., "the benefit-risk balance in the approved indications remains positive"?	New suggested wording: *"…including results of company-sponsored clinical trials…."* With regard to "…at any time…", add a time frame (i.e. within xxx days). Further clarification is needed: Can the language be made more specific about what types of data might be required? Additional studies?
Article 54 Pages 18/19	With respect to additional wording on outer box and PIL for intensively monitored products, we suggest use of a pictogram or symbol to convey the message to patients and physicians, due to limited space on outer cartons. As a fall back position we encourage the use of lay friendly term like "side effects" instead of "serious adverse reactions". Such phrase should also be used in the PIL to make this understandable to patients. We also suggest that a toll-free telephone number or an e-mail address for reports to the MAH is included in the PIL instead of	Suggested revision: "(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) ".* "(oa) *For medicinal products not included on the European list of intensively monitored products referred to in Article 101j, the details on reporting adverse reactions included in the leaflet will*

	the full address. The proposed addition may be interpreted as implying that NO reporting is required for products that are not under intensive monitoring. The presence of material to collect adverse event notifications should be enough to draw attention (presumably much more than an additional row of text on the outer packaging).	*suffice."* In addition, focus panels and public consultation should be conducted to ensure optimal impact of proposed safety reporting reminders that appear on packaging.
Article 59 Page 19	A box with black border could be confusing as compared with Black Box warnings in US labels. Further clarity is required on "key safety information" and "how to minimize risks" – is this foreseen as being a mixture of dosing instructions, contraindications and primary side effects?	Is this another opportunity for transatlantic simplification?
	Directive 2001/83/EC Title IX	
Article 101a Page 20	Paragraph 2: As noted above, the definition of "unexpected adverse reactions" has been marked for deletion from the Directive, although the term is still used in this article. Is this intentional? What types of specific requirements can be imposed on HCPs? Would they be for intensively monitored medicines only? This statement is very broad, and should be clarified. Paragraph 3: How should Member States ensure that such biological medicinal products are identifiable? This could be done in part by providing that biosimilar medicinal products must be given a different INN to the originator medicinal product.	Revise for consistency with Article 1(13), see page 11 of the consultation document. Further, we suggest that the term "unexpected" is useful for both medicinal products and biological medicinal products; consensus definitions should be agreed in global consensus forums. We suggest that the legislation be revised to require that: 1. a distinct INN be assigned to each biologic medicinal product from a different manufacturer; and 2. a physician's agreement is necessary in order to substitute with a different biological medicinal product, whether originator or biosimilar.
Article 101b(1) Page 20/21	The concept of Good Pharmacovigilance Practice (GVP) is interesting and may set a useful threshold for all organizations and individuals that practice pharmacovigilance. We note, however, that the description on pages 20-21 has much overlap	Add greater specificity to the concept of good pharmacovigilance practice to minimize interpretive variability by Member States and National Competent Authorities.

	with requirements for PV 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 what would be in the GVP that would add value rather than just burden, and how patients would benefit or be protected (more than through existing regulations, directives and guidance). There is a risk that the beneficial actions in the proposal that would unburden PV activities by companies and regulators could be neutralized by additional requirements of GVP. It would be helpful to understand what principles are envisaged for GVP and whether GVP might substitute for regulations, directives, and guidance, rather than adding to them. With regard to internationally agreed terminologies, formats of PSURs and protocols and final study reports, it would be preferable if controlled vocabularies and their respective formats were those agreed upon in international consensus forums (e.g., ICH) and if focus of further documents regulating to pharmacovigilance were on **contents** only. Format should not be regionalized to the point of requiring different PSURs for different regions/countries. This may become an unnecessary burden with no positive impact on patient safety protection. If kept, format prescriptions for PASS studies should apply exclusively to non-interventional studies and should preferably deal with the expected table of contents and not with detailed expected formats.	Suggest that this be revised to refer to agreed formats specified in relevant ICH guidelines, e.g., ICH E2C (with Addendum) for PSURs, etc.
Article 101d(2) Page 22	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?	Wording should be added to clarify the continuum between generation of a safety signal hypothesis and steps to confirm a potential signal. The MAH, in consultation with the competent authorities, should be involved in evaluating the potential signal.
Article 101d(3) Page 22	Individual AR reports held on EudraVigilance may be requested by the public. This poses a potential risk of misuse of confidential personal data. It may also encourage use of data out of context. Industry should have access to EudraVigilance data. Article	Consideration should be given to alternative approaches to making safety data available to the public in a meaningful manner.

	101l(4) indicates that the QPPV will have access to the database, but a legal right of access should be afforded to the MAH.	Legal right of access to EudraVigilance should be afforded to the MAH.
Article 101e(1) Page 22/23	"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, inconsistency in reporting among MAHs may result. With regard to causality statement made by "patients or Healthcare Professionals", need to clarify whether these carry equal weight, and whether reports need to be submitted if there are contradictory statements from the patient and HCP (e.g., patient says there is a causal relationship, and their HCP says there is not). More clarity is needed to avoid massive over-reporting, particularly in instances where there is more than one medicinal product or more than one adverse reaction or both in an individual case. The main point to be clarified concerns the distinction of which medicinal product is identified as suspect and which adverse reaction is identified in the report. In addition, "temporal association" should be clarified. Litigation and class action cases and their handling should be clearly separated from other non-HCP cases. Also, see previous comment about using the ICH definition. With regard to the statement "These reports shall be collated at one point within the Community", the intended application of the term "collated" is unclear. These reports should be **accessible** at one point within the Community. Where they are <u>collated</u> would seem to be immaterial. What if regulators from other regions were to ask for the same?	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, and when there are conflicting statements regarding causality. Proposed revision: "Reports where the Patient or Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown, but the *pharmacologically plausible* temporal relationship between the exposure to the identified suspect medicinal product and the identified suspect adverse reaction means that the a causal relationship cannot be excluded." These reports should be *accessible* at one point within the Community.
Article 101e(2) Page 23	As noted in our comments on section 3.2.6 above, the requirement to submit within 15 days all non-serious ADRs that occur in the Community represents a major change in reporting	Propose to continue to submit only serious adverse drug reactions within 15 days. This should apply to reactions within as well as outside of the Community. Non-serious reactions

	obligations and will result in substantial increase in cost for industry and EudraVigilance with no demonstrable benefit to patient safety. In selected EU countries, direct reporting to national authorities implies the inability for the MAH to obtain additional and follow-up information. Some wording around the possibility for the MAH to ask for follow-up and/or additional information for cases originally reported to a national authority would be welcome. In addition, this section should make clear that submission of non-serious reports does not apply to PASS.	should continue to be submitted in aggregate. Include some wording around the possibility for the MAH to ask for follow-up and/or additional information, for cases originally reported to a national authority. In addition, this section should make clear that submission of non-serious reports does not apply to PASS.
Article 101e(3) Page 23	MAH needs to be aware of medication errors as well other ADRs reported to Member Sates on their products. It is not clear how duplicates will be avoided if both the member states and the MAHs will submit to EudraVigilance.	These reports should be made available to MAH.
Article 101e(5) Page 23	Please see previous comments on Section 3.2.6 regarding literature review by EMEA. Regardless of the approach adopted by the Agency, information from literature reports needs to be made available to the MAH.	We suggest that the Commission adopt one of the following approaches: • Limit the proposal for EMEA to scan and data enter case reports from the worldwide published literature to mature, off-patent products. • Specify that EMEA will conduct reviews of the worldwide scientific literature and report literature information to MAHs (including format and timing of such reports).
Article 101f(1) Page 24	What data will be provided to demonstrate the benefit? Does this mean the PSUR will contain more than safety data? We agree with the provision that PSURs should not contain line listings of individual case reports previously submitted to EudraVigilance. However, it is not clear how (or if) this affects the requirements for line listings and tabulations outlined in Volume 9A/ICH E2C. This paragraph also states that PSURs shall contain “all data” related to the volume of sales. This is very broad and not always practical. We suggest that it be clarified as “relevant data” such that not every PSUR need have data broken down by	Ensure update of those documents or ensure language here reflects that the listings required per Volume 9A/ICH E2C are still required. Suggest changing to “all *relevant* data”. Clarify whether sales volume is in addition to exposure calculation (which is largely based on the same data); update

	region, country, age, dose etc. Also, it is not clear how this information is related to the PSUR requirement for exposure calculations. Is it in addition to them, instead of them?	Volume 9A/ICH documents or reference how this requirement relates to exposure requirements in those documents.
Article 101f(2)c Page 24	The term "immediately" requires definition. In addition, the document does not specify the timeframe for submission of a PSUR following the reference date (e.g., 60 days).	
Article 101f (4)(a/b/c) Pages 24/25	The Committee should leverage on the Head of Agencies initiative and the deriving list of reference dates, as agreed between the national authorities and the MAHs and published on the HoAs web site. Starting a new initiative with an independent harmonization effort would be a duplication/repetition of work and by changing what agreed so recently would create unnecessary confusion and rework. Also, regulations have always allowed the use of the International Birth Date (IBD). Going back to European BD 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 international cooperation and information sharing on safety matters more complex, and provide no benefit for public health.	Suggested revision to the second sentence in (a): "…For the purposes of this provision, the European reference date for products containing the same active substance shall be the date of the first authorisation in the Community *or the international birth date* of a medicinal product containing that substance." Suggested revision to the first sentence in (c): "marketing authorisation holders for medicinal products requiring periodic safety update reports may submit requests to the Committee on Pharmacovigilance to change the European reference date or submission schedule for periodic safety update reports *in concert with synchronization initiatives*."
Article 101f (4)(f) Page 25	The review process for PSURs should be modelled on the current process available for CP products, which allows adequate time for discussion and interactions between the MAH and Regulators. http://www.emea.europa.eu/htms/human/postguidance/q78.htm	
Article 101f (4)(h) Page 25	Assessment conclusions may still be preliminary or include requests for additional information. The MAH can respond to assessment reports and the ultimate outcome may be different from what it set forth in the assessment report. For example, the assessment report could suggest 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	We suggest making the final outcome of PSUR assessments and recommendations for changes of product information public, and providing this information in lay language adapted to the audience. Such communications should be made available to the applicable MAH when posted.

	warranted – therefore the public receiving the information at this stage is premature. We support making the final outcome of PSUR assessments and recommendations for changes of product information public, provided that this is done in lay language adapted to the audience. Such communications should be made available to the applicable MAH when posted. However, the assessment report itself should not be made public as this is premature.	
Article101g(1) Page 26	A definition for "serious concern" should be provided, or examples given to establish common grounds as to what would deserve an *ad hoc* PASS across evaluators/agencies.	"Serious" should be defined, or examples given to establish common grounds as to what would deserve an *ad hoc* PASS across evaluators/agencies.
Article 101h(1) Pages 26/27	The requirement for review and approval of protocols for all non-interventional PASS creates some issues when PASS are requested and agreed by other regulatory authorities (e.g., FDA) as a condition of approval, and will include centers within the EEA. This requirement, which in the current Volume 9A is limited to PASS that are part of an RMP or are requested by agencies, seems now 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 requested PASS (or within RMPs), instead of a review of all draft protocols. Clarification of what is considered to "promote the use of a medicinal product" is needed. For example, conducting a PASS of a newly authorized product may involve many investigators who may be using the product for the first time and will gain experience of using the product through the PASS study. Is this considered promotional?	Consider excluding those studies which have been required by another agency. Consider requiring review of draft protocols only for those PASS that are part of RMPs or requested by a CA. Clarify the definition of "promotional" activities.
Article 101i (1)d/h And (2)a Page27/28	These sections provide for posting Risk Management Plans and PASS protocols on the Agency and MS web sites. If the purpose is to increase transparency, summaries providing essential information in an understandable language would	Suggest revising these sections to specify that summaries of the pertinent parts of RMPs and PASS protocols should be posted on the Agency and MS web sites, and that the summaries should be in language readily understood by the lay person.

	seem to be more appropriate than full documents. The current format of RMPs and protocols is not user-friendly and the language and content would be highly technical, with the possibility of misinterpretations or lack of understanding.	
Article 101i (1)f Page 28	Publication of the names of QPPVs in a way that is accessible to the general public could put them at personal risk, e.g., from animal rights activists, patient activists, etc. In addition, there is no benefit to public health, and no need for the public to have this personal information. Therefore, such publication should not take place. QPPV contact details are currently provided to the CAs and the Agency, and this should suffice.	Amend this article as follows: "*(f) A list of the Member States in which the marketing authorisation holder qualified persons for pharmacovigilance reside*."
Article 101i(5) Page 28	The EMEA and PV Committee should drive the risk management plan communication 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.
Article 101i(6) Page 29	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 any personal data.	Proposed revision: "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."
Article 101j	As noted in our comments on section 3.2.6 above, additional clarification regarding the criteria for including a drug on the intensive monitoring list is needed. The list should be an EU-wide list, rather than an MS list. In addition, there should be a specified mechanism for removal of a drug from the list.	The proposed legislation should specify how the public list of medicines subject to intensive monitoring would be established and maintained, and that the list of products under intensive monitoring should be maintained at the EU rather than the MS level. It is imperative that the proposed process be subject to a public consultation period. The proposed legislation, or a future detailed guideline, should specify 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.

Article 101k (1)f Page 29	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.	
Article 101k(6) and (7) Page 30	Relevant manufacturers should always participate when their products are discussed in a public hearing and offer their analysis of the data. The current text simply "allows" participation.	Revise to indicate that the Agency should notify the MAH directly of any public hearing involving their products, and invite their participation in the hearing.
Article 101k (10)d Page 31	Risk minimization actions may be implemented in cooperation with the MAH.	Revise to indicate that risk minimization actions may be implemented "*in cooperation with the MAH*".
Article 101l (1)d Page 31	Will standard methodology be developed for monitoring risk minimization activities by the Agency? What are the implications?	
Article 101l(2) Page 32	With regard to delegation of tasks specified in Articles 101a to 101l, to what extent would delegation apply? Would delegation of any of the tasks imply extension of delegation to decisions on penalties? For example, would one Member State have the power to decide a penalty or levy a fine against a MAH that is a legal entity in a second Member State?	This section should be revised with sensitivity to national sovereignty and general legislation.
Article101l(4)d Page 33	In many non-EU based companies, signal detection in EudraVigilance may be performed by individuals not located in the EU, thus access to EudraVigilance will need to be provided to expert individuals who may reside outside the EEA as delegated by the EU QPPV. Is a separate analysis of data in Eudravigilance requested as compared to an analysis of the full dataset? Is it correct to interpret that in the future all analyses will be conducted on all cases together, irrespective of source, giving the same weight to HCP and non-HCP reports?	The wording in this paragraph must be changed to allow delegation of the list of the activities by the EU QPPV (even outside EEA).
Article 101l	What is the timing of "regular" audits; is there a minimum	Proposed revision: Substitute "audit certificate" for the words

(4)f Page 33	number of audits per time period with which the MAH are expected to comply? Also, audit(s) should be conducted and evidence thereof should be available for inspection, but confidential internal audit reports that include findings should not be available for routine inspection.	"report of the audit" – a certificate may serve as evidence of audit.
	Regulation (EC) 726/2004	
Article 18 Page 42/43	Requirement that, for purposes of inspection, the supervisory authority for pharmacovigilance shall be the competent authorities of the Member State in which the QPPV resides could result in a single member state being overwhelmed with inspections if a lot of companies have its QP residing in a given country, or it could result in companies making QP personnel decisions based on which Member State it wanted to be responsible for inspections. This seems to be a somewhat artificial approach.	It seems that it would be more appropriate to have a supervisory authority that has the expertise for that specific product line than be dependent on where the QPPV lives (although it does facilitate a relationship).
Article 57(2) Page 43/44	In the interests of harmonization, the data from clinical trials should be consistent with the data fields outlined in the WHO standards, and should also conform to data required in the US (clintrials.gov).	The trial data fields should follow international WHO standards. The results database should look to clintrials.gov for opportunities to synchronize.