COMMENTS ON EUROPEAN COMMISSION PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS:

"STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE"

COMMENTS FROM Pfizer to the European Commission (Contact: Mariagrazia Zurlo, +39.02.41498.693, mariagrazia.zurlo@pfizer.com)

GENERAL COMMENTS
The stated goal of this proposed legislation is to strengthen the EU pharmacovigilance system for human medicines. Conceptually, Pfizer supports this goal. Indeed, we appreciate the 2006 consultation, which provided an initial rationalisation for the proposed changes. We believe that the proposed legislation, if enacted, would lead to greater patient safety in the European Union. Also, by stimulating innovation, it would lead to the discovery and development of new therapies for persons for whom there are yet no adequate treatments for their pain, suffering, morbidity, or potential premature mortality. The proposed legislation would meld welfare of the public with excellent policy for Competent Authorities and the private sector. 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. In addition, we are concerned that the proposed legislation would (a) provide a framework for a prescriptive pharmacovigilance system that could have the unintended effect of causing important stakeholders to retreat from valuable dialogue 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.
Europe is part of a global environment. In general, the proposed legislation focuses on harmonization amongst the Member States, but fails to fully consider the advantages to the EU of global harmonization of pharmacovigilance. In some areas, the proposal appears to promote regionalization at the expense of global harmonization with respect to global consensus standards and guidelines agreed by ICH and CIOMS, such as terms and definitions, details of controlled vocabularies for pharmacovigilance, etc.
Pharmacovigilance legislation must consider general legislation. The proposed legislation must be compatible with existing legislation and national sovereignty in other sectors, such as business law.
Science-based methods and transparency are key. This should be explicitly stated in the legislation. If these elements do not take precedence, the process could devolve to political decision-making, hurting patients and innovators. To ensure science and transparency are preeminent, committee structure, types of members, checks and balances, etc., need to be detailed in the legislation.
Bureaucracy should be minimized. Section 101l(2) could increase bureaucracy by giving additional authority over pharmacovigilance to Member States, particularly for monitoring pharmacovigilance and risk minimization measures (despite subsection (g), which calls for participation in harmonization and standardization measures). Additional local authority could result in local interpretive variability, which would not be in the broader interest of public health. If bureaucracy is increased, it will divert resources away from effective pharmacovigilance activities.

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Submit all comments to: by email to peter.arlett@cec.eu.int (or by fax to +32 2 299 8046)
Deadline for comments: <01 February 2008>
These comments and the identity of the sender may be published on the European Commission or EMEA websites unless a specific justified objection is received by the European Commission.

Risk communication to healthcare professionals and patients should be well-balanced. A new "key safety information" section in the SPC highlighting only risks could be very dangerous, as could the proposed "European list of medicines under intense monitoring." The primary danger is that efforts to highlight risks could unnecessarily frighten patients away from needed medicines and discontinuation of a medicine could have more medically serious consequences than the newly highlighted risk. In addition, expected benefits should accompany any communication of risk. At the very least, the communication concepts should be tested carefully as to whether they improve patient health. Patients should be encouraged to consult a healthcare provider before deciding whether or not to discontinue any medication. It will be important to publicly vet the process for establishing and maintaining the list of products subject to intensive monitoring.

SPECIFIC COMMENTS ON TEXT

CONSULTATION SECTION TITLE

Page + Section + Paragraph	**Comment and Rationale (include partial quote of cited text or descriptive reference)**	**Proposed change (as applicable)**
3.2.1 Page 03	*"Within the European Medicines Agency (EMEA), establish a committee (to replace the existing Pharmacovigilance Working Party) with clear responsibility for coordinating pharmacovigilance and for making recommendations on the safety of medicines to the existing Committee on Human Medicinal Products.* *"Rationalise the referral procedures for nationally authorised products: to ensure subsidiarity but also effectiveness have clear obligatory triggers (important safety concerns, including withdrawal of products, restrictions to indications and new contraindications); referrals to have light procedures and public hearings; the output of referrals will be binding Commission decisions to ensure that for important safety issues safety action is taken in all Member States to protect the health of European patients."* 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	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, describe details of the role and interactions of the proposed Committee and ensure public consultation prior to implementation.

	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, including interaction of the Committee with the CHMP and Member States, should be subjected to public consultation prior to implementation.	
3.2.4 Page 05	*"Clarify the existing legal requirement to submit a risk management plan at the time of the marketing authorisation application and make a clearer legal basis for risk management plans, including post-authorisation safety studies to be required when there is a public health concern. Ensure that the key risk management measures are included in the marketing authorisation thereby ensuring that marketing authorisation holders conduct the measures specified and provide updates to the competent authority and the EMEA as specified in the risk management plan.* *"The effect of the clarified legal provisions will be that risk management plans are only submitted when they are needed but that they are fully complied with."* We agree with the position that risk management plans (separate from the SPC) 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.	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 only submitted when they are needed."*
3.2.3 Page 05	*"Simplify the existing requirement for a 'detailed description of the pharmacovigilance system' to be submitted and kept up to date. At marketing authorisation only key elements of the pharmacovigilance system to be submitted as part of the dossier.*	To strengthen this section, wording might be added to explain how the supervisory authority for the QPPV and pharmacovigilance system is envisioned to work in practice and how it would benefit patients.

	"To compensate for reduction in regulatory scrutiny companies will maintain on site a detailed file on their Pharmacovigilance System ("Pharmacovigilance System Master File") and this will be submitted on request by the authorities or can be viewed during inspections. Linked to this there will be a clarification of the legal basis for pharmacovigilance inspections. *"For centrally authorised products create a specific supervisory authority for pharmacovigilance which is the Member State where the company Qualified Person resides."* These provisions are welcomed. However, it would be useful to have an explanation of how the supervisory authority for pharmacovigilance would work and how it would benefit patients. Also, see 101l, p 32.	Also, additional wording might clarify the decision-making process for designation of the supervisory authority for the QPPV and PV System.
3.2.4 Page 06	*"These changes will be a major benefit to public health by ensuring that safety evaluation of products is prospective (i.e. based on risk management planning) and by ensuring that high-quality, EU safety studies are done (i.e. there is compliance) when justified by safety concerns."* It is unclear whether this implies the need for safety studies to be conducted specifically in Europe. Certain safety issues may be more rapidly and sometimes better addressed with multinational studies including non-European countries or even conducted entirely outside of Europe. The limitation to Europe would not seem always scientifically justifiable if the patient population of interest is represented elsewhere and the safety concern is not dependant on medical practice. When scientifically appropriate, it should be possible to conduct safety studies outside the EEA to address EU safety concerns.	We propose additional wording to the effect, " When scientifically appropriate, it should be possible to conduct safety studies outside the EEA to address EU safety concerns."
3.2.5 Page 06	*"Codify guiding principles for the conduct of non-interventional post-authorisation safety studies (i.e. safety studies of marketed products that are not clinical trials). Light oversight (by EMEA pharmacovigilance committee only if conduct to be in more than*	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.

	one Member State) of non-interventional post-authorisation safety studies to ensure that they have health rather than promotional objectives." Non-interventional post-authorisation safety studies – define scope and "light oversight", coordination with Rapporteur / RMS	
3.2.6 Page 06-07	*"Simpler ADR reporting to reduce burden and free up resource:* *» all serious 3rd country reports go to the EU Eudravigilance database only,* *» all EU domestic reports go only to Eudravigilance and thereby to the Member State where they occurred,* *» the EMEA to take on new tasks, clearly defined in scope, for scanning of the scientific literature and entering case reports from the literature on Eudravigilance, rather than the duplication currently conducted by the industry.* *"Regarding medication errors the definition of adverse drug reaction would be clarified as would the reporting rules to make clear that medication errors that result in an adverse reaction should be reported to the competent authorities for medicines (and oblige Member States to ensure any Patient Safety authority is also notified).* *"To increase the proportionality between ADR reporting and the level of knowledge about the safety of a product and to allow a differentiated view of important new medicines, establish a European list of medicines under intensive monitoring: patients and healthcare professionals to be asked to report all suspected ADRs to these products. The EMEA will maintain a public list of intensively monitored products and removal from list will be linked to risk management plan milestones."* *"Make clear the legal basis for patients to report suspected adverse drug reactions:* • *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,*	The language used in all EU-sourced reports in Articles 101d and 101e should make it clear that reports are to be submitted to EudraVigilance in the English language. The proposed legislation should also specify: (a) How medication error reports are to be handled. Primary responsibility for recognising 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; (b) Obligations of EMEA to conduct reviews of the worldwide scientific literature and to report literature information to MAHs (including format and timing of such reports); (c) How the public list of medicines subject to intensive monitoring would be established and maintained. It is imperative that the proposed process be subject to a public consultation period. Postings should include benefits of the product as well as the potential risk being monitored.

	• *for all other drugs reporting via web-sites, directly to the national authority."* Provisions strengthening the role of EudraVigilance as a single, centralised pharmacovigilance database for the EEA are much needed and welcome. All case reports going to EudraVigilance should be in the English language, to save time and costs to regulators and industry. This would also improve the ability of both regulators and industry to analyse aggregate data. 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. Will EMEA report the information gleaned from the literature to MAHs? Who would have responsibility for carrying out searches on local literature and on non-English language literature? Clarifying the reporting of medication errors would likely protect the public health. How this will be done needs to be clarified, though. Would the envisioned public list of intensively monitored products be those that have a formal Risk Management Plan in addition to the SPC and routine pharmacovigilance specification? The process by which the public list is established and maintained should be subjected to public consultation prior to implementation. (Also see 101j, p 29).	
3.2.7 Page 08	*"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."* How are "old" and "established" to be defined, and which body decides? Is this a condition that is to be requested by the MAH, or is it independently granted?	

3.2.7 Page 08	*"…the committee to: make public lists of reference dates for drug substances for the reporting cycle; requests for changes…"* 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 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.	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 Pages 08-09	*"For major safety issues including safety issues affecting drug substances authorised in more than one Member State the legal basis would be clarified for the EMEA committee to coordinate (but not replace) the communications of the Member States."* To avoid contradictory messages on the same issue, we endorse the concept that a single agency, EMEA, would coordinate Safety Communication. *"EMEA should maintain an EU portal on the safety of medicines which would include links to websites of the Member State competent authorities."* We endorse the concept of a single point of entry to public websites of the competent authorities. However, safety portal and 101(k) information should only be disclosed with educational materials and in context with benefit. All concepts regarding design, organisation, and control mechanisms for screening, posting, modifying, and removing content should be subject to public consultation prior to portal implementation.	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.
3.2.8 Pages 09	*"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."* 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.	
3.2.7 Page 08	*"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."* The proposal of not producing PSURs for older products with no safety issues (and often few or no reports) is desirable, as it is very wasteful of resource for both industry and regulators.	Language regarding periodicity of reporting and proportionality to safety, including no PSURs for old established products, should be added to the proposed language under Title IX, Article 101f, 2 d).
3.2.9 Page 09	*"To allow patients to rapidly identify key messages, introduce a new section in the Summary of Product Characteristics and Patient Information Leaflet on 'key safety information' with a transitional phase of 5-years (i.e. update the product information at the time of the next renewal or the next major variation)."* The idea of enhanced selective warnings in SPCs (e.g., a modified 'black box' section) may be beneficial to patients. A practical issue arises in implementing this, however, as there is no assessment tool for selecting what are 'key messages' or 'most important safety information'. These are undefined in current regulatory documents. Indeed, the trigger for 'key' or 'most important' may vary with different products, the indications for use, severity of disease, or prognosis. In addition, what is important to one patient may be less important to another: Highlighting certain safety information may be disadvantageous as it may have the effect of de-emphasizing other essential information, for example, that other patients need. It could also have the effect of 'steering' certain patients toward or away from alternative therapies. If this new section grows to be a substantial	It may be more appropriate for these selected warnings to be displayed on the carton label, when physically practical, and otherwise communicated during prescription or dispensing, so as not to detract from the primary purpose of the SPC as a repository of product information.

	sized section, then it will compete with other information in the SPC, and this could cause confusion or result in patients and prescribers overlooking truly essential information. As a general principle, for the SPC to be an effective reference document, it is best to present safety information in a single place 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 SPC (a) makes it more likely to be read, (b) does not make other information less likely to be read, or (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-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 SPC as a warning document rather than a reference document, and it may be difficult for it to be both.	
Directive 2001/83/EC Article 1(13), 1(16) Page 11	Definitions of unexpected adverse reaction and of abuse are marked for deletion. Why? Common definitions are usually helpful in preventing different interpretations. Moreover, 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.	Suggest that these terms are useful and consensus definitions be agreed in global consensus forums.
Directive 2001/83/EC Article 1(15) Page 12	*"A pharmacoepidemiological study or a clinical trial with an authorised medicinal product ~~in accordance with the terms of the marketing authorisation~~, conducted with the aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product."* 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-authorisation, including those	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 authorisation.

	to explore the drug in new indications or new patient 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 recognise that studies conducted under a risk management plan may include situations not previously studied and, therefore, not strictly within label. However, studies conducted as part of a risk management plan are considered PASS.	
Directive 2001/83/EC Article 8 (3)(ia) Page 12	Directive 2001/83/EC Article 8 (3)(iaa) "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…"	Suggested revision: "…proportionate to the identified potential risks…."
Directive 2001/83/EC Article 8(3)(ia) Page 12	The obligation for the QP 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 QP as an individual, but should be a statement from the applicant company. The QP 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*"
Directive 2001/83/EC Article 8(3)(iaa) Page 13	*"…risk management system shall be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product."* Which body assesses the adequacy of proportionality? What measures will be adopted to guarantee an adequate level of consistency across evaluators?	

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Directive 2001/83/EC Article 23 Page 16	*"In particular, he shall forthwith inform the competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information , including results of clinical trials , which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned."* The request for results of clinical trials should clearly specify that it refers to company-sponsored clinical trials.	New suggested wording: *"…including results of company-sponsored clinical trials…."*
Directive 2001/83/EC Article 54 Pages 18-19	*"The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:* *(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".* 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).	The proposed addition may be interpreted as implying that NO reporting is required for products that are not under intensive monitoring. 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 suffice."* In addition, focus panels and public consultation should be conducted to ensure optimal impact of proposed safety reporting reminders that appear on packaging.
Directive 2001/83/EC Article 101a Page 20	Note that 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?	Revise for consistency with Article 1(13), see page 11 of the consultation document. Further, we suggest that this term is useful for both medicinal products and biological medicinal products; consensus definitions should be agreed in global consensus forums.
Directive 2001/83/EC	"*Through the methods of collecting information and where necessary through the follow up of adverse reaction reports, the MS shall ensure that any biological medicinal product prescribed*	

Article 101a Page 20	*and dispensed in their territory which is the subject of an adverse reaction report is identifiable*." 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.	
Directive 2001/83/EC Article 101b Page 20	*"1. 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 on good pharmacovigilance practice including technical rules and procedures for:"* (etc.) The concept of 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 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 <u>substitute</u> for regulations, directives, and guidance, rather than adding to them.	Add greater specificity to the concept of good pharmacovigilance practise to minimise interpretive variability by Member States and National Competent Authorities.
Directive 2001/83/EC Article 101b Page 21	*"the use of internationally agreed terminologies, including medical terminologies, for mats and standards for the conduct of pharmacovigilance.* ... *"> the format of periodic safety update reports submitted in accordance with Article 101f.* *"> the format of protocols and final study reports for the post - authorisation safety studies referred to in Art 101h."*	Suggested this be revised to refer to agreed formats specified in relevant ICH guidelines, e.g., ICH E2C (with Addendum) for PSURs, etc.

	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 pharmacovigilance were on **contents** only. Format should not be regionalised to the point of requiring different PSURs for different regions/countries. This may become an unnecessary burden with no impact on patient safety protection. If kept, format prescriptions for PASS studies should apply exclusively to non-interventional studies and should preferably deal with expected table of contents and not with detailed expected formats.	
Directive 2001/83/EC Article 101d Page 22	*"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."* 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.
Directive 2001/83/EC Article 101(i)(c) Page 28	*"(c) Information about how to report suspected adverse reactions to medicinal products and forms for their web -based reporting by patients, healthcare professionals and marketing authorisation holders."* All requests for patients to report adverse reactions should also include a recommendation for them to consult their physician.	
Directive 2001/83/EC Article 101e, 1(b) Page 22	*"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 temporal relationship between the exposure to the medicinal product and the adverse reaction means that a causal relationship cannot be*	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 temporal relationship between the exposure to the identified suspect medicinal product and the identified suspect

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	excluded." 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.	adverse reaction means that the a causal relationship cannot be excluded." Litigation and class action cases and their handling should be clearly separated from other non-HCP cases.
Directive 2001/83/EC Article 101e, 1 Page 23	*"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?
Directive 2001/83/EC 101e2, Page 23	*"2. Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15 -days following the receipt of the report, all adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community."* The added value for patient safety protection of the extension of expedited (15-day) reporting to all non-serious EU domestic reports from any source (HCP, non-HCP) is unclear. Extension of the periodic ('PSUR') submission currently required for centrally approved products - with more flexible timelines than those for expedited reports, should suffice. Concentrating resources in quick shipment of non-serious events may be less productive for pharmacovigilance than using the resources freed up by the simplification of reporting to perform follow-up activities on information with greater impact on the public health. 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 also for cases originally reported to a national authority would be welcome.	An explanation of the added value for patient safety protection of the extension of expedited (15-day) reporting to all non-serious reports should be provided. Otherwise, more flexible timelines than for expedited reports should be applied to periodic submission, i.e., 'PSUR' reports, for centrally authorised products. Concentrating resources in quick shipment of non-serious events may be less productive for PV than using the resources freed up by the simplification of reporting in follow-up activities. 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.
Directive 2001/83/EC Article	"*The Agency shall monitor medical literature for reports of adverse reactions to medicinal products for human use authorised or registered in the Community. It shall publish the list of publications*	

101e(5) Page 23	*subject to this monitoring, and it shall enter into Eudravigilance relevant information from the identified literature*." Does this mean that the MAH is relieved of the primary responsibility of performing literature searches for products licensed in the EU? Will the list of publications include all relevant global publications, and if not, will the MAH be obliged to monitor any publications not included on the list? Will the EMEA review non-English language publications and publicise the list of publications reviewed and any modifications that may occur from time to time? Does the MAH have access to their products' cases in Eudravigilance? If these cases are not made available to the MAH it would be impossible to do full benefit/risk analysis and risk management.	
Directive 2001/83/EC Article 101f (4) a/b Page 24	*"4. The following rules shall apply to the submission and assessment of periodic safety update reports:* *(a) the Committee on Pharmacovigilance referred to in Article 56(a)a of Regulation EC(No) 726/2004 may determine the European reference dates and frequency of submission for periodic safety update reports for certain medicinal products for human use authorised in the Community. 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 of a medicinal product containing that substance. The same applies if the date of the first authorisation in the Community cannot be determined .* *(b) the Committee shall draw up and maintain a list of European reference dates and frequency and dates of submission fixed in accordance with point (a) above , which shall be made public by the Agency via the European medicines safety web -portal referred to in Article 10 1i."*	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 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 IBD. Going back to EBD only will create the need for different cut-offs for different countries, i.e. multiple documents with slightly different data sets. This would be very resource intensive, would make international cooperation and information sharing on safety matters more complex.
Directive 2001/83/EC Article 101f	*"The 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."*	Assessment conclusions may still be preliminary or include requests for additional information. Would the publication of work in progress be beneficial for the external community or is there a risk for unnecessary concerns and potentially non-justified actions

(4) h Page 24		with possible detriment? If the latter, assessment conclusions should not be made public.
Directive 2001/83/EC Article 101g (1) Page 26	*"1. The competent authority which granted the marketing authorisation may require a marketing authorisation holder to conduct a post –authorisation safety study if there are serious concerns."*	'Serious' should be defined, or examples given to establish common grounds as to what would deserve an ad hoc PASS across evaluators/agencies.
Directive 2001/83/EC Article 101h (1) c Page 26	*"A draft protocol shall be submitted to the national competent authority for studies to be conducted in only one Member State ,and to the Committee on Pharmacovigilance referred to in Article 56(a)a of Regulation (EC) No 726/2004 for studies to be conducted in more than one Member State."*	This requirement, that in 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.
Directive 2001/83/EC Article 101i(1d/h) And (2a) Page 27	*"(d) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with Regulation (EC) No 726/2004.* *"(h) Agreed post-authorisation safety study protocols, the public abstracts and any recommendations for product information in accordance with Article 101g.* *"2. Each Member State shall set up and update a n ational medicines safety web -portals which shall be linked to the European medicines safety web - portal referred to in paragraph "1. By means of the national medicines safety web -portals, the Member States shall make public at least the following information:* *"(a) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with the procedures of this directive."*	If the purpose is that of increasing transparency, summaries providing essential information in an understandable language would seem to be more appropriate than full documents. Current format of RMPs is not user-friendly and the language and content would be highly technical, with the possibility of misinterpretations or lack of understanding.
Directive 2001/83/EC Article 101i(1)(f)	"*(f) A list of marketing authorisation holder qualified persons for pharmacovigilance and the Member State in which they reside*." Publication of the names of QPs in a way that is accessible to the	Amend this article as follows: "*(f) A list of the Member States in which the marketing authorisation holder qualified persons for pharmacovigilance*

page 28	general public could put them at personal risk, e.g., from animal rights activists. In addition, there is no need for the public to have this personal information. Therefore, such publication should not take place.	*reside*."
Directive 2001/83/EC Article 101i(6) Page 29	*" When the Agency or national competent authorities make information referred to in the previous paragraphs public, any information of a commercially confidential nature shall be deleted unless it s public disclosure is necessary for the protection of public health."* 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 101k (1e) (Chapter 6) Page 29	*"e) it has conducted a pharmacovigilance inspection and found serious deficiencies."*	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. Unclear also how the described community assessment for the evaluation and discussion of safety concerns would also apply to matters of compliance.
Article 101k (6, 7) (Chapter 6) Page 29	*"2. Where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation of a medicinal product. It shall inform the Agency, the Commission and the other Member States no t later than the following working day."*	If urgent action is needed to protect the public health, then information should be provided within **calendar** days
Article 101k (2) (Chapter 6) Page 29	"6. *Following notification under paragraph 1 or 2 , within two working days the Agency shall publicly announce the initiation of the procedure via the web-portal referred to in Article 101i. This announcement shall specify the matter notified, the medicinal product s or substances concerned and how information relevant to the procedure can be submitted . This announcement shall serve to inform marketing authorisation holders and t he public of*	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.

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	the procedure and their right to submit to the Agency information relevant to the procedure. *"Where a public hearing is to be held pursuant to paragraph 7, t he announcement shall include information on the public hearing and how marketing authorisation holders and the public can participate.* *"7. Except when urgent action is required for the protection of public health , the Committee on Pharmacovigilance shall hold a public hearing on the matter notified and marketing authorisation holders and the public may participate by registering following the public announcement of paragraph 5.* *"The Agency shall ensure that all those who register have the opportunity to participate either in person or through the use of web -based technology*."	
Directive 2001/83/EC (Chapter 6) Art 101k Page 30-31	Compliance, even 'serious deficiencies,' should not be cause for public assessment. Information on compliance-oriented internal business process must be evaluated in context with participation of directly involved stakeholders. Corporate competitive knowledge is not a matter for public disclosure, but should be the subject of continuous improvement.	Remove. The provision pertaining to inspections that would allow public assessment should not appear in the legislation.
Directive 2001/83/EC Article 101l(2) Page 32	*"Any of the tasks specified in Article s 101 a to 101l may be delegated by one Member State to another Member State with the written agreement of that Member State. In this event, the delegating Member State shall inform the Commission, the Agency and all other Member States in writing. This information shall be made public by the Member State concerned and by the Agency."* How far would delegation apply? Would delegation of any of the tasks imply extension of delegation of decisions on penalties? For example, would one Member State have the power to decide a penalty for a MAH that is a legal entity in a second Member State?	This section should be revised with sensitivity to national sovereignty and general legislation.
Article 101l (4)	*"d) Monitor all available relevant data including data on Eudravigilance for signals of new or changing risks and for changes to the risk benefit balance of the medicinal product."*	Is a separate analysis of data in Eudravigilance requested as compared to an analysis of the full dataset? Would the MAH have access to Eudravigilance?

(Chapter 7) Page 33		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?
Directive 2001/83/EC Article 101l(4)(f) Page 33	*"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."* What is the timing of "regular" audits; is there a minimum number of audits per time period with which the MAH are expected to comply? 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.	Proposed revision: Substitute "audit certificate" for the words "report of the audit" – a certificate may serve as evidence of audit.