EUROPEAN COMMISSION PUBLIC CONSULTATION
ON THE STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGHTHENING AND RATIONALISING EU PHARMACOVIGILANCE

GENERAL COMMENTS
• Novartis welcomes what in spirit is a pragmatic and proportional approach to managing risk. Assuming these proposed amendments are finalised and agreed to, it is imperative that there is full commitment from the Member State competent authorities to the revised Regulation, Directive and guidelines. If the amendments were to result in further variations of interpretation per country or per competent authority this would merely serve to compound an already complex situation (see Annexes to Volume 9A for examples of non-harmonisation). Therefore, we encourage a review of the final proposal with the specific intent of ensuring that opportunities for Member States to create local regulatory interpretations and deviations from the content is reduced to the greatest extent practicable. • International harmonisation of pharmacovigilance requirements should be an objective in all new or revised regulations and guidance. Regrettably, the proposed legislation reverses existing progress toward a common ICH standard in several areas (e.g. the revised definition of adverse reaction, expedited reporting of non-serious ADRs). ICH definitions should be used to ensure global consistency and optimize the use of industry and health authority resources. • Novartis advocates for comparable pharmacovigilance standards for all biologics, therefore we think that all biotech product (if originator or not) should have the same routine pharmacovigilance obligations. • In order to achieve optimal transparency and communication on safety information, we suggest coordinated and transparent interactions between the EMEA Committees (CHMP, COMP, PDCO, PhVig Com etc.) and interlinkage between the various EU databases, such as Eudravigilance, Eudrapharm etc.). Safety information should be publicly presented in a balanced way considering risks **and** benefits of the product. Therefore, the PhVig Com should coordinate any publication of its safety opinion with the overall scientific assessment and opinion of the CHMP.

Page, Section, Title	Relative Importance	COMMENT AND RATIONALE	PROPOSED CHANGE
Page 3, Section 3.1 Legislative Strategy	**High**	Assuming the proposals to amend Directive 2001/83/EC and Regulation 726/2004 are adopted it is imperative to plan for corresponding amendments to the guidance presented in Volume 9A (last updated April 2007). This is vital for both Marketing Authorisation Holders and the competent authorities as: 1. Volume 9A is tightly bound to the legislation which is to be amended, and 2. Volume 9A forms the basis of the	Ensure that the proposals provide for resource to support amendments to Volume 9A in parallel with changes to Directive 2001/83/EC and Regulation 726/2004 as well as with the Variation Regulation in order to capture safety variations/ label changes for nationally registered products in the same way as for products registered via CP or MRP/DCP. Specify a timeline for the revision and publication of a significant update to Volume 9A, ideally in close temporal

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		documentation used for inspections.	association with, but certainly not later than 3 months after, the adoption of the amended Regulation and Directive.
Page 3 Section 3.2.1 Fast robust decision-making	**Medium**	How would the new committee 'coordinate pharmacovigilance and make recommendations'? Depending on the final definition of roles and responsibilities of this Committee, the ability to cope with its future workload and potential delays of decisions caused by the high workload should be considered and addressed. Furthermore, it should be clarified how the new Committee will coordinate their assessment on safety with the CHMP which is the only committee which generates the scientific opinion based on overall risk:benefit.	This appears to be what currently happens within the EU PhVWP, but there is significant lack of harmonisation at present. A more robust decision-making body is required. Thus, this committee (as the others within the EMEA) should have a legal basis for coordinating Pharmacovigilance beyond the Member States for all authorised products in the EU, independently from their registration pathway. Names of members, rules of procedures etc. should be published on the EMEA website. There should be the possibility for the industry to have meetings with the Committee, the possibility for appeal etc. Coordinated interaction between the EMEA Committees is needed in order to ensure the publication of balanced opinions on medicinal products.
Page 4 Section 3.2.1 Fast robust decision-making "Why", 2nd paragraph	**Medium**	"Current legal provisions on referrals are unclear and overlapping and the use of the provisions is limited." The provisions laid down in Directive 2001/83/EC Art 29-34 are very clear. No modification of the legislation in this respect needed.	Improvement of referral procedures triggered by pharmacovigilance information may be achieved by a coordinating role assumed by the future Pharmacovigilance Committee. The outcome of the referrals should be binding for all affected products in the EU and its implementation should be followed up by the new PhVig Committee.
Page 4 Section 3.2.1 Fast robust decision-making "Impact", 3rd paragraph	**Medium**	What is understood as robustness may vary to a high degree according to the type of a drug and the knowledge already gathered.	Proposed additional wording: "….. directly linked to robustness of post-authorisation pharmacovigilance **with the requirements of post-authorization PV being adaptable to product specificities and to already accumulated knowledge regarding the respective API."**

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Page 4, Section 3.2.2 Clarify / codify roles and responsibilities and codify standards for industry and regulators	**Medium**	"Poor compliance" is cited as a justification of the proposed amendments.	Please cite supporting evidence, as compliance (in terms of expedited and periodic reporting) by this MAH is exemplary.
EU QPPV role	**Medium**	Require more details on which roles and responsibilities to be codified / clarified. (Greater focus on role of EU QPPV?)	It is difficult to envisage how the MAH EU QPPV role could be more defined as it is already done in Vol 9A. However, a similar role for the member state competent authorities would be valued by MAHs, such that there is a counterpart with the agencies.
GVP	**Medium**	Establish concept of Good Vigilance Practice - create legal basis for a regulation on GVP.	Need clearer outline of how (practically) this is planned and how it will be implemented and enforced. It also should be in line with ICH E2D. Clarification is also needed on whether the GVP concept will be laid down in a guideline or in a document with more binding character.
Page 5, Section 3.2.3 Simplify informing the authorities about the company pharmacovigilance system	**High**	It should be noted that the claimed simplification of the content of the MAA may have a compensatory increase in complexity for MAHs. If the phrase *on site* is interpreted to mean that a 'Pharmacovigilance System Master File' must be kept at each of the MAH's national affiliates, the overall effect would be to generate more documentation rather than less. Also, the first paragraph of 3.2.3 concerning the elements of the pharmacovigilance system to be submitted with the dossier appears to contradict the scope of the text on page 12, Article 8(3)(iaa). "For centrally authorised products create a specific supervisory authority for pharmacovigilance which is the Member State where the company Qualified Person resides"	Reduce the burden of documentation by requiring only a Summary of Pharmacovigilance System in the MA. The production of a Pharmacovigilance System Master File and a Detailed Description of Risk Management System should be required periodically – say every two years or upon request from a competent authority or prior to an inspection. The documents should either be submitted to the EMEA and made available to other Member State competent authorities directly from the EMEA, or it should suffice to retain a single file in the country where the QPPV's office is located or at the European headquarters. Clarify scope. All products authorised in more than one Member State

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		It is not clear why such an authority should focus on centrally authorised products only. This authority could assume a coordination role amongst the member states for inspections.	should be covered independently of their type of registration. Clear roles and responsibility of the supervisory authority should be defined.
Page 6 Section 3.2.5 Codify non-interventional safety studies **RELATED TOPIC:** **Page 11/12 Directive 2001/83/EC Article 1(15) Definition of PASS**	**High**	The proposed definition of Post-Authorisation Safety Study (PASS) remains ambiguous and now appears to be much broader in scope with the addition of the last statement: "…or confirming the safety profile of the drug." Change text '… conducted with the aim of identifying, characterising or quantifying a safety hazard...'	Limit the definition of PASS to studies conducted in accordance with the terms of the marketing authorisation with safety as a **primary** objective, including non-EU studies which have been requested by an authority as part of the product's risk management plan. '… conducted with the **primary** aim of identifying, characterising or quantifying a safety hazard...'
Page 6, Section 3.2.5 Codify non-interventional safety studies	**High**	Concerning the legal mandate for PASS studies Will this ensure that commitments made at authorisation are honoured? How will this be done? If PASS studies fail to get off the ground due to low recruitment numbers, for example, it is difficult to envisage how such a position can be recovered. What does "light oversight" entail? - submission of periodic reports? Approving the protocols? End of study reports? Also, in the last paragraph of the section, the meaning of "that risk management plans are only submitted when they are needed" is confusing. Are they not needed with virtually every new marketing application? This language could be interpreted to mean that they are not.	There must be a pragmatic response to PASS studies that do not achieve the stipulated goals. In many cases recruitment targets can simply not be achieved if the anticipated market share is not achieved. Please clarify the meaning of "light oversight". Clarify when risk management plans are needed.

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Page 6, Section 3.2.6 Simplify and make proportional reporting of single serious adverse drug reaction (ADR) case reports **Also: Page 7, 7th paragraph** **Literature screening**	**High**	Scanning scientific literature on behalf of MAHs is an excellent initiative, but there must be a system for informing MAHs of new cases so that non EMEA compliance obligations can be met. Unless a rapid, robust and foolproof system is in place, all MAHs will be forced to continue literature screening in order to meet the requirements of ex-EU regulators. Some practicalities of this provision are not completely clear: How will MAHs get knowledge of or access to reports entered to Eudravigilance in the context of literature scanning? How to ensure that the screening is complete? Who is in charge of the assessment of findings? Who pays for this service, and how much? In addition, it should be noted that global pharmaceutical companies will **still need to perform such activities to meet the requirements of health authorities outside the EU**. Therefore, an alerting process for the global literature may not be practical. Furthermore, even if industry would not have to report cases to EMEA, it would still be ethically obliged to review the literature on its products.	The EMEA could identify a list of local European journals for which it will take the responsibility to perform screening and rapidly alert MAHs of new ADRs. Industry should review scientific literature and report cases to EMEA. EMEA should enter case reports, avoiding duplication. However, it has to be ensured that a provision is made for MAH access to or alerting of scientific literature for its drugs. It may be possible to establish a process whereby the EMEA could take responsibility for local European journals and assign global literature screening to a single MAH. In any case, if EMEA is in charge of literature screening, it should also be done in compliance with FDA requirements. A clarification for literature search for generic companies is needed. We recommend that generic companies do not need to do literature search.
Page 6/7: EudraVigilance and Electronic Reporting	**Medium**	The commitment to EudraVigilance and electronic reporting is notable, but what percentage of all ADRs in Europe are reported electronically? Can the current MAH systems and those of the competent authorities support this proposal?	This needs to be supported by rigorous enforcement of electronic reporting by MAHs (not currently a finding on inspection), plus the transition of all competent authorities who do not currently accept electronic reports from MAHs to ensure that their systems are ICH-compliant. Reporting into the Eudravigilance database should be done in English.
Page 7, 2nd paragraph	**Medium**	"Regarding medication errors the definition of	Clarification of intent is required.

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Medication errors (1)		adverse drug reaction would be clarified….." Would this definition include all medication error scenarios such as maladministration, accidental exposure, dispensing errors, overdose etc ?	
Medication errors (2)	**Medium**	This proposal indicates that all medication errors resulting in an ADR are potentially expeditable.	There should be a distinction made between medication errors resulting in a serious outcome (or potential errors that may have resulted in a serious outcome) and all other reports of medication errors. Only medication errors (or potential errors) resulting in a serious outcome (or that could have resulted in a serious outcome) should be expeditable. A series of scenarios should be defined in the updated version of Volume 9A to help clarify how to handle reports of medication errors.
Page 7, 3rd paragraph: **Intensive Surveillance of new medicines**	**High**	It is unclear from the proposal whether the requirement for intensive surveillance will apply to all new medicines. It could result either in a biased over- or under- reporting of ADRs, depending on the audience and how it interprets the meaning of intensive surveillance. It is unclear when and how the requirement for intensive surveillance will be reassessed and subsequently removed when a safety profile has been established. "EMEA will maintain a public link of intensively monitored products." It is unclear how this will be administered and which drugs it will be applied to. How will patients and health professionals be alerted to this list apart from SmPC/PIL? (Process similar to Black Triangle?) Who is in charge of the maintenance of this list?	Clarify the application of the requirement for intensive surveillance. It's meaning and objectives should be disclosed to all stakeholder audiences. Clarify the periodicity for reassessment of this requirement (suggest every 3 years to coincide with PSUR periodicity, or on application by MAH with submission of a PSUR plus addendum with bridging report e.g. at 3 years and 6 months, or 4 years etc.). Clarify the criteria for removal of the requirement for intensive surveillance. Provide further guidance on the intended process. Please provide a definition for "new medicines".
Page 7, 4th paragraph	**High**	Limiting all domestic EU reports "to go only into	The EC must take steps to mandate the use of

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Eudravigilance		Eudravigilance" is an excellent simplification initiative.	Eudravigilance and to ensure there is commitment from all Member States to adopt the requirement. Otherwise, complexity and costs will increase for all parties involved in the process.
Page 7, 5th paragraph **Patient Reporting** **Related topic pg. 22 Directive 2001/83/EC, Article 101e**	**Medium**	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. Impact for packaging and extra cost. Is there any evidence that such a system will 1- increase reporting from patients or indeed? 2- provide better quality data? Article 101e is very problematic and confusing; **1a** Requires the submission of adverse reactions for reports where the *patient* or the health care professional has made a statement of possible attribution for spontaneous reports (currently, the health professional attribution is used). This will create a new EU requirement for MAHs to submit non-HCP cases as individual reports. Is the intent to rely on consumer causality as part of the ADR reporting paradigm? This has significant implications for the number and quality of reports in Eudravigilance. **1b** Requires the submission of all reports where no causality statement is made or the causality is unknown. This has negative connotations, particularly if it is intended to include observational studies, for which it is often rate to	Urgent clarification is required concerning the purpose, mechanisms and scope of patient ADR reporting, which appears to be new and is currently not an EU requirement. We strongly recommend that spontaneous report and observational study assessments as part of the reporting paradigm are limited to health professionals, as patients are not qualified to make such evaluations. In general, companies should apply a conservative approach in the assessment of causality for cases with missing reporter causality. However, their decisions should be based on medical and scientific assessment, (e.g. events or outcomes which are expected in high morbidity or mortality populations could be assessed as non-suspected in the absence of a reporter causality). To consider all cases with missing reporter causality as 'suspected' is very problematic, as reflected in the comments and rationale.

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		receive a causality statement from the treating physician. MAHs are often required to conduct epidemiology studies, product usage surveys, and other observational activities for which extensive medical data and reporter causality are lacking and follow-up is not possible. This requirement could lead to a significant over-expediting of relatively low-value cases, particularly if the MAH is not given the legal means to use medical judgment in assessing the possible causality in the absence of a treating physician's attribution statement. In addition, encouraging patient reports may reduce the incentive for health providers to submit ADRs. It can also lead to situations where patient and provider submit two dissimilar and conflicting versions of the same report.	
Page 7, Section 3.2.6 5th paragraph	**Medium**	Patient reports to go to MAH on paper form included with PIL for intensively monitored drugs. All other drugs reported via web-sites to the national authority. The addition of a ADR form in the box will lead to significant costs, because a bigger box is needed to fit the additional paper with consequences for storage and shipping. Furthermore, it may be difficult to provide a multi-language form for e.g. Belgium or other countries.	There should be no requirement to include a ADR reporting form in the box. In the case of the requirement of patient reporting ADR forms, there should be standardisation as to where and how reports are sent as different reporting systems may result in different patterns and quality of reported ICSRs. Signals from healthcare professional reports may be diluted by large numbers of low-quality non-serious reports from patients.
Page 7, 7th paragraph Screening literature	**High**	Please refer to the comments and proposals provided for: **Page 6, Section 3.2.6 Simplify and make proportional reporting of**	Please refer to the comments and proposals provided for: **Page 6, Section 3.2.6 Simplify and make proportional reporting of single**

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		single serious adverse drug reaction (ADR) case reports	**serious adverse drug reaction (ADR) case reports**
Page 8, Section 3.2.7 Simplify and make proportional to risk periodic safety update report submission by industry (PSURs)	**High**	The concept of "linking" a PSUR to risk management planning has basic merit, but it is not possible to comment on it due to the complete absence of regulatory guidance on this topic. It has also to be considered that approval dates vary from one region to the other (US, EU). It may not be desirable to universally abandon PSURs for products > 10 years old, as new information concerning both benefits and safety risks does arise with older products, resulting in changes to the overall risk-benefit profile. Products >10 years old may also be approved for new indications. All products with a specific RMP require a PSUR. It is important to define a harmonised single standard for the whole of Europe.	Provide specific details on how "linking" would work. Please specify when the 10-year period begins (from first approval? From newest indication?), since approvals between the regions (US, EU) may differ significantly and new indications have the potential to reset the clock. Industry to file an executive summary PSUR for all products > 10 years old. All products with a specific risk management plan must have a PSUR prepared according to the time period set down in the legislation or otherwise agreed with the Health Authority. Also recommend strengthening the proposal to the greatest extent possible to minimise the opportunity for Member States to impose reporting timeframes, intervals, and content that are not synchronised with the rest of the EU. Obligations to provide a PSUR should not be dependent on whether they belong to a certain application type (namely generic, biosimilar, well-established, herbal, homeopathic), they should be linked to the existence of a specific RMP.
Electronic Reporting of PSURs	**Medium**	Electronic reporting of PSURs has no defined standards or processes.	Define, test and implement standards for electronic reporting of PSURs.
Assessment of PSURs	**Medium**	How will feedback be provided to the MAH? What is the timeframe for PSUR assessment reports to be completed? (Must be less than 4 months in order to allow MAH to respond in next PSUR).	Clarify the working of the EU PSUR Assessment Group and specify the timelines for assessment reports to be completed and sent to the MAH.
Page 8;		Generally acceptable.	

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Impact, 2nd paragraph		It should be stressed, however, that cost savings on industry side will be balanced by increased costs for higher frequency of necessary variations and SmPC revisions and may be more frequent Direct Health Care Professional Communications (DHCPCs).	
Page 9, Section 3.2.8 Strengthen medicines safety transparency and communication 4th paragraph	**Medium**	Legal provisions on the provision of information on the EU drug dictionary are unnecessary.	This should be aligned with ICH M5 and maintained as guidance rather than legislation.
Page 9, Section 3.2.9 Clearer Safety Warnings in product information to improve the safe use of medicines	**High**	Substantial re-work involved in revising all SmPCs and PLs. How will MAHs and competent authorities provide education to stakeholders (prescribers and patients) such that new safety warnings are not viewed with such caution that beneficial medicines are withheld or patients become non-compliant due to safety concerns? Potentially useful but the devil as always is in the details of execution. The proposal appears akin to 'black box' warnings as in the US, is it envisaged that there will be global alignment of prescribing information? In order to improve compliance with prescribed medicinal therapy and to avoid undue under- or non-compliance not only scaring but better balanced information should be presented to patients by adding a chapter on key benefits of the API to the product information.	This requires substantial effort to ensure that stakeholders are educated and prepared for the proposed changes to SmPCs and PLs, otherwise it may result in potentially beneficial medication being withheld by the prescriber, or non-compliance by the patient. Modifying the text of SmPC and PL for all authorised products will cause a huge workload and high costs for the industry (working time, printing, fees for variation procedures etc). Ensure sufficient transition period for the MAH to meet the obligation for changing all SmPCs and PLs and confirm that no re-packaging of products already on the market is needed (high costs!). This exercise should be in line with provisions of the currently discussed amendment of the Variation Regulation (which proposes e.g. Grouping of variations).
Page 11, Directive 2001/83/EC Article 1(11) Definition of ADR	**High**	The definition of Adverse Reaction is too broad as written and does not distinguish between the concepts of ‘reaction’ and ‘event’. If this is	The current ICH definition of adverse reactions should be retained. If this standard is no longer appropriate, a revised definition should be developed through ICH

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		applied to observational studies, where it is often rare to receive a causality assessment from the treating physician, this could lead to a significant over-expediting of relatively low-value cases, particularly if the MAH is not given the legal means to use medical judgment in assessing possible causality in the absence of a treating physician's attribution statement.	consensus.
Page 12, Directive 2001/83/EC Article 1(15) Post-authorisation safety study	**High**	**Please see comments under:** **Page 5,6 Section 3.2.5 Codify non-interventional safety studies** **RELATED TOPIC:** **Page 11/12 Directive 2001/83/EC Article 1(15) Definition of PASS**	**Please see comments under:** **Page 5,6 Section 3.2.5 Codify non-interventional safety studies** **RELATED TOPIC:** **Page 11/12 Directive 2001/83/EC Article 1(15) Definition of PASS**
Page 12, Directive 2001/83/EC Article 1(33)	**Medium**	The use of "System" for both the company general pharmacovigilance activities ("pharmacovigilance system") as well as the specific activities for a product ("risk management system") will lead to confusion.	Clearer definition for the term "system" needed.
Page 12, Directive 2001/83/EC Article 8 (3)(iaa),	**Medium**	In "3.2.4 Impact" it is specified that Risk Management Plans are only to be submitted when they are needed.	Proposed amendment: Insert at the very beginning: **If applicable a detailed description of the** …. *(see p. 6 Impact, paragraph 2)*
Page 13, Directive 2001/83/EC Article 11 **new 4)**	**Medium**	A balance between safety and efficacy information should be provided in order to avoid alarming patients and risk their compliance.	after *3. pharmaceutical form* a new number should be inserted: **4. key benefit information about the medicinal product.**

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			The next number should then be: 5. *key safety information ….*
Page 13, Directive 2001/83/EC Article 11, 3b	**Medium**	Since key safety information is already described in section 4.8 of the SmPC both in the introduction and in the table, what will a further description in section 3b bring? Refer also to comments under "**Page 9, Section 3.2.9, Clearer Safety Warnings in product information to improve the safe use of medicines"** With regard to the additional statement "This medicinal product is under intensive monitoring…."	Replace 3b) by **5)**. A statement in section 3b directing the reader to section 4.8 should suffice. Clarification needed what exactly 'key safety information' is? Who decides, based on what criteria? Information on criteria applied for products being under intensive monitoring needed. Whereas such an information is of value for health care professionals, it is questionable whether patients are not made unsure or even worried taking this medicine and thus, getting incompliant.
Page 14, Directive 2001/83/EC Article 21, bullet 1	**Medium**	"The risk management *system* shall be annexed to the marketing authorisation…" *System* and *plan* are used interchangeable throughout document (e.g. Article 101i Chapter 5 page 28 states risk management *plan*)	Ensure consistency – if there is an intended distinction between the terms it should be clarified.
Page 14, Directive 2001/83/EC Article 21 bullet 1, 2nd paragraph	**Medium**	The RMP is a large detailed document with potential proprietary information. It is not necessary to add the entire document to the MA.	The newly inserted sentence at the end of *1. When the marketing authorization ……* should be amended to read as follows: The risk management system shall be annexed to the marketing authorization**, if applicable**. *(see p. 6 Impact, paragraph 2)* However, the summary table of the RMP should suffice for attachment to the MA.
Page 14, Directive 2001/83/EC Article 21, bullet 3	**Medium**	Clarification is needed concerning what part of the Marketing Authorisation will be made public. We have concern over proprietary information being released and also over privacy concerns if	Define components of the MA to be made public.

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		the names of a MAH's employees are made public.	
Page 14, Directive 2001/83/EC Article 21, bullet 4	**Medium**	Refer to comment under **Page 14, Directive 2001/83/EC Article 21 bullet 1, 2nd paragraph**	4. The competent authorities …line 4: … clinical trials and **if applicable** as regards the risk …
Page 15, Directive 2001/83/EC, Article 22, bullet 1	**Medium**	By deleting the statement of exceptional circumstances in order to legislate for RMPs for all products, the EC has deleted the basis for "approval under exceptional circumstances".	Article 14(8) should not be deleted. The text for stating that products can be approved subject to renewable conditions should be made in a separate paragraph.
Page 16, Directive 2001/83/EC Article 23	**Medium**	General references to "he" (here and throughout document). Should these not refer to the MAH?	Text should not be gender-specific.
Page 16, Directive 2001/83/EC Article 23, 4th paragraph	**Medium**	"… shall ensure that the product information is kept up to date …. including assessment conclusions made public via the European medicines safety web-portal …"	Information is needed on how to practically align information between product information and the European medicines safety web-portal.
Page 16, Directive 2001/83/EC Article 23, last paragraph	**Medium**	Any action regarding a variation to the MAA/MA should be avoided. Thus a MAA should only give reference to the DDPV Master File to be submitted to and be accessible at the EMEA (see also p. 5, 3.2.3)	The newly inserted sentence at the end of the article should be replaced by the following: **The current version of the pharmacovigilance system master file should be submitted to and be accessible for competent authorities at the EMEA.**
Page 17, Reg 726/2004 Article 16	**Medium**	"The competent authority may at any time ask the holder of the marketing authorisation to submit a copy of the pharmacovigilance system master file".	Clarify the expected timeframe for submission by the MAH.
Page 19, Directive 2001/83/EC Article 54	**Medium**	By including the statement about reporting suspected ARs only for some products this could create confusion that ARs should not be reported for the others. Patients also may not understand the difference between "suspected" and other ARs.	Please modify text as follows: "… the following statement shall be included " All ~~suspected~~ adverse reactions should be reported (see leaflet for details)".
Page 19, Directive 2001/83/EC Article 59,	**High**	Please refer to comments already made under: **Page 9, Section 3.2.9, Clearer Safety**	Please refer to comments already made under: **Page 9, Section 3.2.9, Clearer Safety Warnings in**

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Section 1 (ba) **key safety information & intensively monitoring**		**Warnings in product information to improve the safe use of medicines"** and **Page 13, Directive 2001/83/EC Article 11, 3b** The proposed use of a box surrounded by a black border reminds of the "black box warnings" typically used in the US in case of very serious risks. Explanation of reason(s) for intensive monitoring may be helpful in reducing anxiety with the patients and improving safety data reported.	**product information to improve the safe use of medicines"** and **Page 13, Directive 2001/83/EC Article 11, 3b** No surrounding box should be used, at least not in black. Other ways of distinctions from the remaining text may be more appropriate, such as different style of writing. Explanatory text would be of value when specifying the reasons for subjecting a new medicine to intensive monitoring. As proposed above: *(ba)* should be replaced by (d) with an additional paragraph placed before: (c) key benefit information about the medicinal product
Page 20, Directive 2001/83/EC Article 101a **heading and 3rd paragraph**	**Medium**	The requirements for the reporting of ADR should be the same for all medicinal products independently if they are of chemical or biological origin. That means via adverse reaction reports all medicinal products should be identifiable in order to take appropriate action.	Proposal for a modified wording: "Reporting of adverse reactions by healthcare professionals and identification of ~~biological~~ medicinal products which are the subject of adverse reaction reports Article 101a … … Through the methods of collection information … ensure that any ~~biological~~ medicinal product prescribed and dispensed … is identifiable."
Page 20, Directive 2001/83/EC Title IX, Article 101a, 2nd paragraph	**Medium**	Where is "unexpected" defined? According to the revision of Article 1(13) (see page 11) it is foreseen to delete the definition, at	Please provide definition for "unexpected".

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		least than given there.	
Page 22, Article 101d 3	**Medium**	The comment on ADR reports requested by the public and provided by the agency is unclear. How will the data be presented and in what context? And in which language ? The national implementation of this paragraph will be impossible in most of the MSs without a specific agreement of the patient concerned (privacy protection of electronic data) Access to complete ADR-reports for everybody including persons without any kind of experience in the field of pharmacovigilance is the root cause of misunderstanding and misinterpretation.	The release of data should be accompanied by clear disclaimers that put it into the appropriate medical context. Delete requirements for individual patient reports.
Page 22, Article 101d 3	**Medium**	"The MAH shall accept reports of adverse reactions electronically". It is unclear if this applies only to ADRs from regulators or from the public also. Is the intent that MAHs create on-line reporting tools for the general public and educate them in how to perform data entry?	Clarify the scope of this requirement.
Page 23, Article 101e, Data Management and Reporting/ bullet 2 – expediting non-serious cases	**High**	"MAH's shall submit electronically to Eudravigilance no later than *15 days* following the receipt of the report, **all** ADRs that occur in the community…." One can understand why these should be populated in Eudravigilance for signal detection purposes but not clear why rapid reporting has been extended to non serious reports that occur in the Community. This represents a major process change for MAHs that negates the purpose of conducting case triage to process and transmit the most important cases first. It greatly restricts the ability of MAHs to managed fluctuations in workload, as there will	We strongly recommend to drop the requirement for expedited reporting of non-serious cases . Please adhere to requirements for ADR submission laid down in Vol 9A. Please consider one or more of the following options in line with E2B requirements: • Ongoing electronic E2B submission as cases are locked per the MAH's processing timeframe . • Electronic E2B submission at the time of PSUR submission. Restrict any expediting requirement to spontaneous reports.

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		no longer be any flexibility to postpone non-serious processing for short periods of time when workload is high. More costs will arise for more resources to cope with the increased expedited data entry. This significant impact is further compounded by the proposal's absence of language specifically excluding non-serious reports from observational studies. Such data is inherently low in quality, has not been vetted by the treating physician, and is not stored in the safety database by MAHs. To do so is an inefficient use of resources that could better be deployed on activities with higher value.	
Page 23, Article 101e, Data Management and Reporting/ bullet 2	**Medium**	"These reports will be made available to the Member States through Eudravigilance. Does this requirement also mean that no additional reporting to national Competent Authorities is needed, since they all have access to the Eudravigilance database?	Please clarify.
Page 23, Article 101e, bullet 2	**Medium**	'submit electronically … all adverse reactions that occur in the community…'	Clarification requested – does this really mean "all"?
Page 23, Article 101e, bullet 3, 2nd paragraph	**Medium**	"… each Member State shall accept reports of adverse reaction via their websites which shall be linked to the European medicines safety web-portal…"	Please indicate a timeframe by when Member States shall have the proposed web-tools/technology running.
Page 23, Article 101e, bullet 3, 3rd paragraph	**Medium**	Proposed wording is difficult to understand, therefore an easier to read text is needed.	Proposal to rearrange paragraph 3: the last break should read as follows: The Member States shall ensure **that the national competent authorities for medicinal products are notified of any adverse reactions brought to the attention of national competent authorities for patient safety. They shall also ensure that reports of medication errors brought to their attention in the**

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			framework of adverse reaction reporting for medicinal products are made available to any national competent authority for patient safety within that Member State.
Page 23, Article 101e, bullet 3, bullet 5, 2nd paragraph	**Medium**	If MAHs do not have access to the reports documented in Eudravigilance connected to EMEA literature screening then they would have to go on with their own parallel literature screening.	Proposal to amend paragraph 5: The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the conduct of medical literature monitoring, entry of relevant information into Eudravigilance, **and the access of MAHs to the information entered to Eudravigilance regarding their products.**
Page 24, Article 101f, bullet 1	**Medium**	"Marketing authorisation holder shall submit periodic safety update reports (PSURs) to the Agency …" Does this mean no additional submission of PSURs to individual Competent Authorities is necessary? PSURs should not contain "all data" on sales and "any data" on prescription volume. This would legally oblige inclusion of huge amounts of information.	Please clarify. Proposal to amend wording: "reliable data" on sales and prescription volume
Page 24, Article 101f, bullet 4a	**Medium**	…the Committee on Pharmacovigilance referred to in Article 56(a) of Regulation EC(No) 726/2004 may determine ….for certain medicinal products for human use authorised in the Community…"	The scope of this article should be clarified, i.e. are all medicinal products authorised in the EU independent from their registration pathway included? Please refer also to comments under **Page 3 Section 3.2.1** **Fast robust decision-making**
Page 24, Article 101f,	**Medium**		3rd line:

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bullet 4a			"active substance" should be replaced by the commonly used "active **pharmaceutical ingredient**".
Page 24, Article 101f, bullet 4b	**Medium**	The creation of an additional listing with potentially differing or conflicting dates should be avoided where a respective listing is already in existence.	Right at the beginning the wording should be amended as follows: **Unless already available through the listings of harmonised birthdates** the Committee shall …
Page 28, Directive 2001/83/EC Article 101i, bullet 1f	**High**	The agency shall make public a list of MAH QPPVs for pharmacovigilance and member state where they reside. We have strong objection to this list being made public. It is a violation of personal and data privacy and will expose QPPVs to unwarranted attention from individuals with harmful intent, such as animal rights activists. The personal safety of the QPPV should not be compromised by posting information that has no benefit to the public health.	The QPPV list should be made available to health authorities, no added value for this list to be made public. The current wording should be revised as follows: A list of marketing authorisation holders **and their contact data.**
Page 28, Directive 2001/83/EC Article 101i, bullet 2	**Medium**	"Each Member State shall set up and update a national medicines safety web-portal which shall be linked to the European medicines safety web-portal…"	Please indicate a timeframe by when Member States shall have the proposed web-tools/technology running
Page 29, Directive 2001/83/EC Article 101i, bullet 6	**Medium**	Not only commercially but also personally confidential information, e.g. full names and addresses, must be protected	The 2nd part of the sentence should read as follows: Any information of a commercially **or personally** confidential nature shall ……
Page 30, Article 101k, bullet 1, 1st line	**Medium**	The MAH should be informed at the same time than all other interested parties	The text should read as follows: A Member State shall notify the other Member States, the Agency, the Commission **and except for d) also the marketing authorisation holder** and shall …….
Page 30, Article 101k,	**Medium**	bullet 4 is missing	

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bullet 4			
Page 30, Article 101k, bullet 5, 1st line	**Medium**	The MAH should be informed at the same time than all other interested parties	The text should read as follows: …. The Member State shall make available to the Agency **and the marketing authorisation holder** all scientific information …..
Page 30, Article 101k, bullet 7 and 8	**Medium**	"… the Committee on Pharmacovigilance shall hold a public hearing on the matter notified and marketing _uthorization holders…." "… he may request to present those data to the Committee on Pharmacovigilance in a non-public hearing."	Please provide guidance on the procedure for public and non-public hearings. Replace "he" by Marketing Authorisation Holder.
Page 31, Article 101k, bullet 12, 1st line	**Medium**	A decision that no further evaluation or action is required is a decision as well. This should be communicated.	The text should read as follows: **According to** paragraph 10 **a) or 10 b)** the Commission shall adopt a ……
Page 31, Article 101l, bullet 1 c)	**Medium**	there is no initial schedule specified here. Should for 1 (c) the same apply than for 2 (h) of this article?	
Page 33, Article 101l, 4(a)	**Medium**	The wording "the competent authority" is imprecise. It should be clarified whether the CA of the QPPV's country of residence is meant or the CA of the country where the MAH resides.	The last sentence should read as follows: The name and the contact details of the qualified person (QPPV) shall be notified to the competent authority **of the QPPV's country of residence** and the agency.
Page 33, Article 110l, 4(d)	**Medium**	"MAH shall monitor all available relevant data on *Eudravigilance* for signals on new or changing risks….". It is unclear why it is incumbent on MAH to monitor Eudravigilance and how far this requirement extends (e.g. to other products in same class?) What form of access will be provided? How can signal detection be	Further clarification is required on responsibility of MAH to monitor Eudravigilance for signals as such data are already available with the marketing authorisation documentation..

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		performed by MAH on this dataset?	
Page 33, Article 101l, 4(f) Audit reports	**High**	Objection is made to the requirement for placing company's audit findings in Pharmacovigilance System Master File. Such reports are confidential company information and there is no benefit to releasing them to an external audience.	It should be sufficient for a MAH to present evidence that audits are being conducted in accordance with a defined internal plan and that corrective actions are taken in a timely manner. The text should read as follows: Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices and **ensure preparation of and follow up on an action plan according to the audit results.**
Page 37, Directive 2001/83/EC, Article 111 1d)	**High**	GMP Inspections: "Inspect the premises, records and documents including the *pharmacovigilance system master file*…". Is pharmacovigilance therefore in scope for every GMP inspection? Does a master file have to be located in every MAH manufacturing site?	Clarification on scope of GMP inspections is required. Where should the pharmacovigilance master file be located? We recommend only one master file for all types of marketing authorization held at QPPV office as per comment above for Section 3.2.3
Page 39, Directive 2001/83/EC, Article 111, new bullet 8	**Medium**	Nothing is specified within this new paragraph regarding the issuance of a MAH-comment to the audit report prepared by the authority.	Place the following text at the beginning of paragraph 8: **The Competent Authority of the Member State compiles a draft report on the audit results inclusive of all uncovered deficiencies and provides the MAH with the draft version. Within 3 weeks after receipt the MAH may comment on the contents of the draft report. Subsequently the CA compiles the final report which either takes the MAH-comments into account or at least gives reference to dissenting opinions. All final PV inspection reports shall be sent by the Member states** to the agency. If the outcome of …….
Page 39, Directive 2001/83/EC Articles 116	**Medium**	Why is "under normal/authorised conditions of use" deleted?	Please restore.

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and 117			
Page 40, Directive 2001/83/EC, Article 117 (3)	**Medium**	"…..limit the prohibition to supply the product to new patients".	Clarification / rewrite of this text. Is it meant to mean that the prohibition would apply to new patients who had not had previous treatment with a given drug or drug class?
Page 43, Regulation (EC) No 726/2004 Article 57(2), paragraph 2 (b):	**Medium**	The current wording leaves in the worst case only 12 months of time for the preparation of the complete medicinal product information. This rather short period of time would place a high burden of workload on all big generic companies.	The current wording should be revised as follows: (b) by -/- (eighteen months after **this format has been published by the agency)** marketing authorisation holders …….
Page 44, Regulation (EC) No 726/2004 Article 61 (1 and 2), paragraph 2 (b):	**Medium**	Comment to newly added specification regarding the constitution of the Committee on Pharmacovigilance (end of paragraph 1, 1st break and new 2 (a) and (b)): Being composed of one member from each of the countries belonging to the Community and 4 additional members, to be appointed by the Commission, this committee would be a giant one with a total number of 31 members currently and further increase in the future through additional countries joining the EU.	A far better approach would be a committee with a maximum of 15 members including the ones to be appointed by the Commission. The member states should be represented by 5 standing and another 6 annually or biannually rotating members.

The proposals on clarification of:

Page 5 Section 3.2.4 Rationalise Risk Management Planning Post-Authorisation Conditions (PAC)
Page 6, Section 3.2.5 Codify oversight of non-interventional studies Post-Authorisation Safety Studies (PASS)
Page 6, Section 3.2.6 Simplify and make proportional reporting of single serious adverse drug reaction (ADR) case reports Reporting of all EU domestic reports and all serious third country ICSRs to EudraVigilance only are welcomed as positive steps to improve the status quo.