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PART II: DETAILED EMEA COMMENTS ON PROPOSED LEGISLATION

COMMENTS ON PROPOSALS FOR DIRECTIVE 2001/83/EC

Article	Proposed text	Comment
Article 1(11)	Definition of adverse reaction	***Proposed change:*** To revise definition: A noxious response to a medicinal product which occurs when using the product within or outside the terms of the summary of product characteristics. ***Justification:*** It is very welcomed to broaden the scope of the definition as proposed by the EC, which will reflect actual pharmacovigilance practice. It should be considered to broaden the definition even more and to delete "and unintended". Adverse reactions may be the result of an intended overdose, e.g. suicidal or criminal intention. In order to ensure that the scope of the definition covers reactions after any use, including abuse, a revision of the definition drafted by the EC is proposed. See also EMEA comment 17 on key proposals for legislative change.
Article 1(13)	Deletion of definition of Unexpected adverse reaction	***Proposed change:*** The Commission should clarify its intention regarding unexpected reactions. It is proposed either to remove any mention of unexpected reactions in the text of the Legislation (it is still mentioned in Article 101a), or to keep the concept and revise the existing definition as follows: An adverse reaction, the nature, severity, frequency, risk factors or outcome of which is not consistent with the summary of product characteristics. ***Justification:*** The EC proposes to delete this definition, probably because it is not needed anymore for reporting, given the new requirements proposed by the EC in this respect. The term is however still included in Article 101a. It should also be remembered that the concept

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		is also used in the current description of a signal and relates to concepts such as knowledge on the safety profile versus unknown aspects, changes of risk-benefit balance and missing information in RMPs. It is therefore proposed to keep and extend the current definition by the elements of frequency and risk factors.
Article 1(15)	Definition of Post-authorisation safety study	***Proposed change:*** To revise the final definition as proposed by the PhVWP/EMEA experts (available in Q1 2008). The current draft is as follows: A clinical trial carried out in accordance with the terms of marketing authorisation or an observational pharmacoepidemiological study, conducted to evaluate safety relating to an authorised medicinal product. The new proposal needs to be very careful and precise in the terms used so that they are compatible with Dir 2001/20/EC. It should also be clear if the intention of this new legislation is to amend or simply to be complementary to Dir 2001/20/EC. ***Justification:*** See also EMEA comment 12 on key proposals for legislative change. Post-authorisation safety studies are defined by their primary objective (ie studies conducted after the authorisation in accordance with the terms of the Marketing Authorisation aimed to better characterise the risks associated with the use of medicines). The methodology of the study is a different issue, PASS can be either interventional or observational (even if they are mostly observational). The current definition of PASS is unclear, in addition there is a possible overlap with the supervision of interventional clinical trials in accordance with Directive 2001/20/EC resulting in a duplication of work and possible confusion in the roles and responsibilities. The definition of a clinical trial and of a non-interventional clinical trial are given in Directive 2001/20/EC. Non-interventional CTs are excluded from the scope of Dir 2001/20/EC. The review of the legislation should lead to an overview of observational studies by the new Pharmacovigilance forum to avoid the conduct of promotional studies. Finally, a different proposal for the revision of PASS has recently been considered in depth by experts from the PhVWP/EMEA but is not yet finalised. It is proposed to include the definition once finalised. In any case, there is a need for a consistent terminology throughout the text.
Article 1(16)	Deletion of the definition of abuse	***Proposed change:*** It is proposed to maintain such definition as the term is still used in Article 71(2) of

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		Directive 2001/83/EC and it is now proposed to be included in Article 101a. This does not affect the fact that the definition of adverse reaction has been broadened.
Article 1(33)	Definition of Risk Management System	***Proposed change:*** It is proposed to replace "System" by "Plan". It is also proposed to replace "interventions" with risk minimisation activities". The following definition is proposed: "Risk Management Plan: a set of pharmacovigilance and risk minimisation activities designed to identify, characterise, prevent or minimise risks relating to a specific medicinal product, including the assessment of the effectiveness of those activities." ***Justification:*** See also EMEA comment 11 on key proposals for legislative change. The dual terminology "Risk Management System" and "Risk Management Plan" should be removed. There is one system, the Pharmacovigilance system, which is company-specific and provides the infrastructure and procedures for the routine and additional pharmacovigilance activities for each product. Risk management is product-specific, and to call it a "system" is confusing. Deletion of the terminology "Risk Management System" would also avoid confusion in designating the Risk Management Plan.
Article 8(3)(ia)		***Proposed change:*** To clarify the meaning of "site of Pharmacovigilance System Master File". ***Justification:*** Is the 'site of Pharmacovigilance System Master File' a unique site that holds the Master File? Or is it held at all sites where pharmacovigilance activities are performed? Shall it be linked to the QPPV site?
Article 8(3)(iaa)	A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce. This risk management system shall be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product.	***Proposed change:*** The notion of "proportionality" is not considered necessary and the second sentence could be deleted. If the Commission wishes to keep it, the following revision for the paragraph is proposed: "A detailed description of the pharmacovigilance system, and, where appropriate, a Risk Management Plan which the applicant will introduce. The pharmacovigilance and risk minimisation activities within the Risk Management Plan

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		shall be proportionate to the identified risks, potential risks and need for additional safety data." ***Justification:*** At the time of submission of the RMP, the identified and potential risks are not yet known from regulatory authorities and the proposed text is not helpful in deciding whether to submit or not a RMP and the importance of the RMP. In addition, the implementation of ICH E2E requires the submission of a safety specification and Pharmacovigilance plan, and a safety specification cannot be proportionate. If "proportionate" relates to the submission or non-submission of a RMP, it may even be questioned if the concept of proportionality is needed at all in the legislation. It is also proposed to the EC to consider that risk management is concerned not only with identified and potential risks but also with missing information. In Volume 9A, missing information is defined as follows: Information about the safety of a medicinal product which is not available at the time of submission of the EU Risk Management Plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace. The concept of missing information is of particular importance e.g. for advanced therapy medicinal products. Overall, risk management should, inter alia, aim at reducing uncertainty, hence obtaining additional data as needed on identified and potential risks and new data on areas of missing information.
Article 11(3)(b) (to be corrected to a)	key safety information about the medicinal product and how to minimise risks. For medicinal products included on the European list of intensively monitored products referred to in Article 101j this information shall also include the statement "This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported.	***Proposed change:*** To be revised to: Summary of key information about the medicinal product. The content of the summary will be defined in a Guideline. For medicinal products included on the European list of intensively monitored products referred to in Article 101j this information shall also include the statement "This medicinal product is under intensive monitoring and reporting of suspected adverse reactions is of particular importance". ***Justification:*** See EMEA comment 25 on key proposals for legislative change.

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Article 21(1)	The risk management system shall be annexed to the marketing authorisation.	***Proposed change:*** Only the Summary Table of the Risk Management Plan should be annexed and the sentence should be changed as follows: "A summary table of the pharmacovigilance and risk minimisation activities included in the Risk Management Plan shall be annexed to the marketing authorisation. Details of the Summary Table will be specified in a guideline". ***Justification:*** See also EMEA comment 11 on key proposals for legislative change. The European Commission's proposal is not supported: - it is contradictory with the principle of the RMP to be a living document which is frequently updated, for example at defined milestones - a variation would need to be submitted whenever the MAH updates the RMP, for ex. whenever it amends study protocols - obligations to the MAH relate to the pharmacovigilance and risk minimisation activities, not to the safety specification included in the RMP - if annexed to the marketing authorisation, the RMP would have to be translated in all languages (with its annexes, the RMP sometimes contain >1000 pages!) - there is a risk to have a high bureaucratic and burdensome situation regarding changes - in the update of the Guideline on the Risk Management System, it can be specified with more details the format and content of the Summary Table.
Article 21(2)	… to ensure that the information given in the summary is in conformity with…	***Proposed change:*** To clarify the summary referred to. Does this relate to the Summary of Product Characteristics?
Article 21(4)	… and as regards the risk management system…	***Proposed change:*** To delete the reference to the Risk Management System in the text, but, if it is maintained, to replace "Risk Management System" with "Risk Management Plan…"and add reference to the Pharmacovigilance Master File.

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		Justification: It is understood that the Risk Management System/Plan assessment is part of the QSE assessment and therefore we do not see the need to specify it in this article. However, if it is added, reference to the Pharmacovigilance System Master File would also be needed and these would need to be reflected in the suspension and withdrawal provisions.
Article 21(4)	"The justification shall be provided separately for each indication applied for."	***Proposed change:*** To clarify that the justification applies to the deletion of confidential information.
Article 22	Changes to MA under exceptional circumstances	***Proposed change:*** In summary, the following is proposed: - To maintain the concept of a MA under exceptional circumstances. - Provisions should be made to allow the inclusion of any authorised medicinal product in the list of intensively monitored products at any time (pre and post-authorisation), and to remove it from the list when the CHMP considers it is not any more necessary to have it in. ***Justification:*** See also EMEA comment 12 on key proposals for legislative change. Although the concept of intensively-monitored products is supported, it seems that the existing option of MA under Exceptional Circumstances is proposed to be replaced by a type of intensively monitored MAs with RMPs. The concept of exceptional circumstances should be maintained as it is needed for situations where efficacy data are incomplete. It may specially impact on advanced therapy medicinal products and orphan drugs. The proposed modification of this article can in fact be applicable to any medicinal product. If deadlines are mentioned in the MA and there is a need to modify them, variations will be required and this is against the principle of administrative simplification.
Article 22(1)	"A marketing authorisation may be granted subject to the following conditions, included in the risk management system: (a) the requirement to conduct post-authorisation safety studies , or,	***Proposed change:*** 1. ~~In exceptional circumstances and following consultation with the applicant, the authorisation~~ **Where necessary, a**~~A~~ marketing authorisation may be granted **or amended** subject to the following conditions **of intensive monitoring**, included in the risk management ~~**system**~~**plan**: ~~may be granted subject to a requirement for the app~~

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	(b) adverse reaction recording or reporting that differs from the requirements of Title IX, or, (c) any conditions or restrictions with regard to the safe and effective use of the medicinal product . The marketing authorisation shall lay down dead -lines for the fulfilment of the conditions where necessary. Continuation of the authorisation shall be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions."	~~licant to meet certain conditions, in particular : concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible without delay, to gether with deadlines and dates of fulfilment.~~ (a) the requirement to conduct **certain** post-authorisation safety studies , **and**/or, (b) adverse reaction recording or reporting that differs from the requirements of Title IX, **and**/or, **(c) ~~any~~ certain** conditions or restrictions with regard to the safe and effective use of the medicinal product. The marketing authorisation shall lay down dead-lines for the fulfilment of the conditions where necessary. Continuation of the authorisation shall be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions. *[Please note that when the corresponding article of Regulation (EC) no 726/2004 is drafted, account should be taken of conditional approval and 1 year renewal to avoid confusion regarding the conditions]* 2. The Member States shall notify to the Agency the granting of marketing authorisations **or subsequent post-authorisation procedures which introduce such ~~subject to~~** conditions as referred to in paragraph 1 and these medicinal products shall be included in the European list of intensively monitored products referred to in Article 101j. A medicinal product shall be removed from the list when the competent authority which granted **or amended** the marketing authorisation concludes that the measures referred to in paragraph 1 have been completed **or are no longer necessary** and that, following the assessment of any data resulting from the implementation of the conditions, the benefit -risk balance remains positive.

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		Justification: - Deletion of the word "granted" allows to broaden the scope of the intensively-monitoring procedure to authorised products. - "Risk Management System" is replaced by Risk Management Plan - Given the uncertainty regarding the definition of PASS and the possibility that the definition will be broadened, it is considered that not all PASS should be *de facto* linked to the intensively-monitored status, hence the word "certain". The same reasoning applies to conditions or restrictions of use. The Committee should take the decision for including the product in the list of intensively-monitored products, with a justification. - Conditions or restrictions include specific reporting criteria or risk minimisation activities (e.g. educational programme) that have to be carried out as long as the product is on the market and therefore which will never be "completed". Does it mean that those products will remain on the list of intensively monitored products for ever, even if there are no more safety concerns? It is proposed that the competent authority may decide to remove a product on the list when some measures are no longer necessary.
Article 23, 4th paragraph	Updated information on medicines safety web-portal	Since the MAH is not responsible for the Competent Authorities' (CA) assessment and the medicines safety web-portal, it seems strange to make the MAH responsible for keeping the product information up-to-date as it seems being proposed by the EC. There is a need to clarify the responsibilities.
Article 26	Deletion of : (b) its therapeutic efficacy is insufficiently substantiated by the applicant;	***Proposed change:*** Either to maintain the Article as it is, or to keep only the first condition: the risk-benefit balance is not considered to be favourable. ***Justification:*** It is not clear why, in the context of the legislation revision for strengthening pharmacovigilance, the condition of an insufficiently substantiated therapeutic efficacy has been deleted. It is understood that this condition is included in the concept of risk-benefit balance, but this is also the case for quality issues.

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Article 54(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) ".	***Proposed change:*** The outer packaging for many medicinal products is not large enough to allow inclusion of that statement, especially in countries with more than one national language. The statement should be replaced with a pictogram, with the mention "see leaflet".
Article 59 (1)(ba)	key safety information about the medicinal product and how to minimise risks. This information shall be presented in a box surrounded by a black border. F or medicinal products included on the European list of intensively monitored products referred to in Article 101j the following additional statement shall be included "This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to < the name and address of the marketing authorisation holder in the Member State where the marketing authorisation hold er will receive suspected adverse reaction reports >"	***Proposed change:*** To revise to: "Summary of key information about the medicinal product. The content of the summary will be defined in a Guideline. This information shall be presented in a box surrounded by a black border. For medicinal products included on the European list of intensively monitored products referred to in Article 101j the following additional statement shall be included: "This medicinal product is under intensive monitoring and reporting of side effects is of particular importance". ***Justification:*** See also justification for Article 11(3) (b). As regards the reporting to MAHs, see also EMEA comment 16 on key proposals for legislative change.
Article 101a, 3rd paragraph	Biologicals identifiability	Provisions for product identifiability are very welcomed. The EC proposes that MS should ensure this for biologicals. The EC is asked to consider providing MS with additional supporting provisions by allocating responsibilities in this respect to MAHs (in line with Volume 9A rev autumn 2007). It should also be considered applying distribution documentation to all medicinal products for assessment of reporting clusters and impact assessment of batch recalls (in terms of product availability and need to ensure availability of alternative treatment; these points are also important to be communicated to the public when announcing a major batch recall).
Article 101a	Deletion of description of MS/EU pharmacovigilance system	***Proposed change:*** To add: Member States shall operate a system for the fulfilment of their pharmacovigilance tasks and participation in the EU pharmacovigilance system. This system of surveillance of authorised medicinal products shall be used to collect information on the risks of medicinal products as regards patients' or public health, including information on misuse and abuse. The information collected shall

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		particularly refer to adverse reactions in human beings, arising from use of the product within the terms of the marketing authorisation as well as from any other use, including overdose, misuse, abuse, erroneous use, and those occurring after occupational exposure. The system shall evaluate all information scientifically, consider options of risk minimisation and prevention of adverse reaction and take regulatory action as necessary. ***Justification:*** The current Article 102 allocates the responsibility of operating pharmacovigilance systems to MS. The Legislative Proposals of the EC allocate pharmacovigilance tasks to MS and requires each MS to designate a competent authority for pharmacovigilance in Article 101l (2) (a). What is however now missing in the Directive is a description of pharmacovigilance and its objectives. It should be clear in the legislation that pharmacovigilance assesses risks associated with medicinal products not only with their use within the terms of the SPC but also associated with e.g. off-label use/overdose or overuse/misuse/abuse/error/occupational exposure. This seems to be intended by the EC, as the proposed broadening of scope of the adverse reaction definition and new reference to medication error shows. Consideration should therefore be given to add an explicit statement enforcing this approach. This is important, also because the statement in the current Article 102 ("This system shall take into account any available information on misuse and abuse…") is not included in Article 101 and the following articles of the EC Legislative Proposals.
Article 101b, Title	Title: Good Vigilance Practice	***Proposed change:*** To change the title to "Good pharmacovigilance practice". To find an acronym. ***Justification:*** "Good pharmacovigilance practice" is mentioned in the text and should also be used in the title. It would be useful to have an acronym e.g. GVP, GPVP or GPhVP (given that GPP stands for Good Pharmacy Practices, setting standards for dispensing and patient counselling).

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Article 101b(1)	Good Vigilance Practice	***Proposed changes:*** ***Good Pharmacovigilance Practice*** Article 101b 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 including technical rules and procedures and publish them in Volume 9A of the Rules Governing Medicinal Products in the EU. These guidelines shall relate to: a. Good Pharmacovigilance Practice: Good pharmacovigilance practice is a set of principles and guidelines setting out scientific and technical quality standards for the operation of pharmacovigilance systems and the conduct of pharmacovigilance by Marketing Authorisation Holders and competent authorities. Principles of good pharmacovigilance practice are set out in article 101. The guidelines on good pharmacovigilance practice shall include: • The establishment and operation of the pharmacovigilance system including the responsibilities and arrangements for: o expedited reporting o periodic reporting o signal detection o risk management and mitigation. • The quality assurance and quality control necessary to ensure the proper functioning of the pharmacovigilance system and the quality of the data and reports produced. • Provisions including the quality management, organisation, management, personnel, training, written procedures, use of data bases and related electronic systems, documentation, archive, and audit of the pharmacovigilance system. • The establishment, content and maintenance of the pharmacovigilance system master file. o The role and responsibilities of the:

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		▪ marketing authorization holder ▪ qualified person for pharmacovigilance ▪ competent authorities. The good pharmacovigilance practice may be supplemented by annexes addressing specific topics as required. b. Scientific and technical standards for the conduct of pharmacovigilance including: • The use of internationally agreed terminologies, including medical terminologies, formats and standards for the conduct of pharmacovigilance. • The electronic reporting of adverse reactions and the submission of reports to Eudravigilance in accordance with Article101e. • The monitoring by the Agency of the data in Eudravigilance for signals of new or changing risks in accordance with 101d. • The format of periodic safety update reports submitted in accordance with Article 101f. • The format of protocols and final study reports for the post-authorisation safety studies referred to in Art 101h. c. Regulatory guidelines on the operation of pharmacovigilance including: • Procedures and formats for drug safety communications including the procedures for management of urgent communications in accordance with Article 101i. • The operation of Article 101k. • Scientific and procedural guidelines on audit by the Marketing Authorisation Holders, National Competent Authorities and Agency of their performance of pharmacovigilance. 2. These guidelines shall be revised and supplemented as necessary to take account of technical, scientific and regulatory progress.

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		3. Marketing authorisation holders, the Agency and the competent authorities shall follow the guidelines referred to in paragraph 1 in the fulfilment of their tasks related to pharmacovigilance. 4. The measures adopted shall take account of international harmonisation work carried out in the field of pharmacovigilance. ***Justification:*** GVP is a quality management tool. It therefore seems appropriate to include scientific principles for pharmacovigilance. A very important aspect of any GXP is to establish principles and detailed guidance on the quality assurance and control systems and the responsibility for the quality and operation of the systems. There should, in the Regulation/ Directive, be clear provisions for quality assurance and quality control and auditing system in place, including written procedures as a first bullet point before the technical pharmacovigilance issues that are bulleted. It would be helpful if the EC could clarify if the GVP would be a revised and expanded version of Volume 9A. In favour of good regulatory practice, the concept of Volume 9A as a complete and consistent format for the pharmacovigilance guidelines in the EU should be continued and GVP be integrated in Volume 9A. In (3), it is assumed that 'measures' refer to the guidelines mentioned in the article.
Article 101c	Independence	***Proposed change:*** To revise to: The management of funds intended for activities connected with pharmacovigilance at the level of competent authorities, … ***Justification:*** It seems that this Article refers to the funds available to competent authorities. If so, this could be specified for clarity.
Article 101d(1)		***Proposed change:*** When referring to 'medicinal products authorised in accordance with Article 6(1)', the European Commission should clarify if this includes all medicinal products (MPs) i.e. traditional herbal MPs and homeopathic MPs regardless of route of authorisation (i.e.

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		registration procedure).Article 16g should make reference to the new Articles.
Article 101d(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	***Proposed change:*** To revise to: 'The Agency, the Member State Competent Authorities and the Marketing Authorisation Holders shall monitor the data in Eudravigilance for signals of new or changing risks of medicinal products authorised in the Community. The Commission shall be informed of any important information on pharmacovigilance in accordance with Article 101i.' ***Justification:*** Article 101l on responsibilities and tasks mentions the monitoring of data in Eudravigilance as a task also to be performed by MS and MAHs. As the procedure for communication of information is mentioned in Article 101i, reference is made to that article. See also EMEA comment 16 on key proposals for legislative change.
Article 101d(3)	Individual adverse reaction reports held on the Eudravigilance database may be requested by the public and these data shall be provided by the Agency or the national competent authority from whom they were requested within 90 -days unless this would compromise the anonymity of the subjects of the reports.	***Proposed change:*** Please rephrase as follows: " Individual adverse reaction reports held on the Eudravigilance database as reported in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 may be requested by the public and these data shall be provided by the Agency or the national competent authority from whom they were requested within 90 days unless this will compromise the anonymity of patients. Any disclosure of data should be in accordance with personal data protection legislation". It is proposed to also keep the current sentence of Article 26(3) of Regulation 726/2004 which states that EudraVigilance data shall be made publicly accessible, if relevant, after evaluation. ***Justification*** See EMEA comment 22 on key proposals for legislative change, in particular as regards the proactive disclosure of data.

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Article 101e(1)	Recording and reporting of adverse drug reactions by Marketing Authorisation Holders	***Proposed change:*** To revise Art 101e(1) as follows: Marketing Authorisation Holders shall record all **reports of suspected** adverse reactions in the Community or in third countries which are brought to their attention. **Reports of suspected** adverse reactions recorded shall be reports where the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility, and this shall include: (a) Reports where the Patient or the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; and (b) Reports where the Patient or the Healthcare Professional has not made any statement on 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~~ **for which** a causal relationship can not be excluded. The Marketing Authorisation Holder shall accept reports of **suspected** adverse reactions electronically. ~~These~~ **Reports of suspected adverse reactions** shall be collated at one point within the Community by the Marketing Authorisation Holder. ***Justification:*** The EC proposes to specify that adverse reactions refer to cases where a causal relationship is considered to be at least a reasonable possibility. However, the concept of "considered to be at least a reasonable possibility" refers to the suspicion and the evaluation of the cases rather than the adverse reaction itself which is already defined as a response (i.e. causally related) in Article 1 (11). In order to introduce the text from Volume 9A regarding reporter statements, as proposed by the EC, it is proposed to refer to "Reports of suspected adverse reaction". Throughout the legal text "suspected" should be added before "adverse reaction", as applicable. The reference to "temporal relationship" has been removed, because it may be subject

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		to different interpretations. The sentence "These reports shall be collated at one point within the Community." should be extended by "by the marketing authorisation holder", as it might otherwise sound as if all MAHs should have one point within the Community. It should also be made clear that the sentence "These reports shall be collated at one point within the Community." refers to reports where the MAH considers that a causal relationship is at least a reasonable possibility, and not to reports of adverse reactions received electronically. "Reports of suspected adverse reactions" has been added.
Article 101e(2)	Deletion of reporting of suspected transmission of an infectious agent via a medicinal product	***Proposed change:*** To re-introduce reporting requirement for suspected transmission of an infectious agent via a medicinal product. To change "all adverse reactions" to "all suspected adverse reactions" and "all serious adverse reactions" to "all serious suspected adverse reactions". ***Justification:*** This current reporting requirement seems to have been missed in the EC Legislative Proposals. This reporting requirement for suspected transmission of an infectious agent via a medicinal product should be re-introduced in this article (or alternatively be added to the definition of adverse reaction).
Article 101e(2)	Expedited reporting of non-serious reactions	***Proposed change:*** Periodic reporting should be considered for non-serious reactions, within the time frame of the PSUR or yearly, whatever is more frequent. ***Justification:*** The need for this newly proposed expedited reporting requirement for non-serious reactions should be discussed with view to efficiency of the system. A periodic reporting could be considered instead.
Article 101e(3)		***Proposed change***: The third paragraph should be clarified. It should be made clearer that this concerns exchange of information between national competent authorities across all Member States.

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Article 101e(5)	Screening of medical literature by the Agency	***Proposed change:*** The EC proposal is not supported. See EMEA comment 16 on key proposals for legislative change.
Article 101e (6)	World Heath Organization	***Proposed change:*** To correct "s" to "z" in this and other articles (Article 101): World Health Organization. To add the sentence: "Any sharing of information should be in accordance with personal data protection legislation". In addition, the EMEA would like the European Commission to consider in its impact assessment the technical consequences of retransmitting reports.
Article 101f(3)	PSUR exemptions	The Commission's proposal is supported. However, the EC might reflect on a possible alternative tool to have the MAHs of products with PSUR exemption to perform a cumulative review of the safety profile of these products on a regular basis, and inform competent authorities of the results of such evaluation. See also EMEA comment 20 on key proposals for legislative change.
Article 101f(4(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.	***Proposed change:*** It is proposed to add: "The change of frequency of submission for periodic safety update reports shall be justified." ***Justification:*** It is anticipated that, in many cases, PSURs will be requested with a higher frequency as a precautionary measure. It should be specified that the change of frequency should be duly justified by the Regulatory Authorities. Reference should be made to Article 56(1)(aa) as per proposed amendment.
Article 101f(4)(c)		***Proposed change:*** It is proposed that the change of the reference date and submission schedule is independent of the Variation Regulation and the CHMP. The procedure for such change may be defined by the CMD(h).
Article 101f(4)(f)	Timetable	***Proposed change:*** It is suggested that the proposed timetable should follow the current timetable for the

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		centralised procedure, and all delays should be shortened. The delay for the initial PSUR assessment report may be reduced to 30 days. ***Justification:*** The current timetable for assessing PSURs is 60 days. In accordance with the current proposals the proposed procedure and timetable for assessing PSURs is far too long (i.e. 90 + 30 + 30 = 150 days!!). Moreover, the outcome of PSUR assessments often leads to requests for cumulative analyses, follow up of reported cases and other requirements to be included in the following PSUR. The proposed assessment timetable will make this impossible.
Article 101f(4)(i)	Competent authorities and marketing authorisation holders shall take account of the recommendations for the product information.	***Proposed change:*** To be revised to: "Competent authorities and marketing authorisation holders **shall act upon** the recommendations for the product information **within 60 days unless otherwise agreed**." ***Justification:*** Need to reinforce the implementation of recommendations of published recommendations, with a timetable. Otherwise the assessment procedure may lose credibility.
Article 101h		***Proposed change:*** It is suggested that an impact assessment of this procedure is carried out. ***Justification:*** See also EMEA comment 13 on key proposals for legislative change. There are many non-interventional safety studies started every month in the EU or elsewhere. Although there is no obligatory assessment of the protocols, there will be a huge administrative task imposed on both Member States and EMEA, as well as on the industry. This requires proper impact assessment.
Article 101h(1)(c)		***Proposed change:*** Reference should be made to Article 56(1)(aa) as per proposed amendment.
Article 101h (1) (d)	Objection to PASS	***Proposed change:***

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		To revise to: In the event that …. objects to the study protocol because it is considered to fall under the scope of Directive 2001/20/EC, or because the conduct of the study is considered to promote the use of a medicinal product, *or* **because the design of the study is considered not to fulfil the study objectives or to provide the data needed to investigate the safety concern at issue**, the marketing authorisation holder … ***Justification:*** Another reason for objecting to a PASS protocol may be that the study is not designed to deliver the data required and address the safety concern appropriately.
Article 101h (1) (i)	Impact of PASS results	***Proposed change:*** To revise "product labelling" to: "terms of the marketing authorisation, in particular the product information". Applies also to Article 101i (1) (h). ***Justification:*** "product labelling" could be extended to "terms of the marketing authorisation, in particular the product information".
Article 101h (j)	In addition to any reporting requirements in the study protocol, the marketing authorization holder shall submit an abstract of the study results to the Committee. The Committee may decide that the abstract is made public via the European medicines safety web –portal referred to in Article 10 1i or, after the agreement of the marketing authorization holder, may decided that an amended abstract shall be made public.	***Proposed change:*** It is proposed to specify that the MAHs shall submit electronically to the Agency an abstract of the studies. The Agency will propose to the "Medicines Safety Advisory Board" the list of abstracts to be made public. This forum will discuss abstracts for which changes are proposed by the Agency. ***Justification:*** Given the large number of studies considered as PASS conducted anywhere, this provision may induce a huge administrative task for the forum in charge of such topic. It is an impossible task to revise the abstract submitted for each study and assess its concordance with the study reports, and, in addition, agree/negotiate with the MAH whenever changes are made.
Article 101i	European medicines safety webportal	The proposed publications in a European medicines safety web-portal are agreed. Nevertheless, attention should be paid to ensure: - accessibility of the information to the public (e.g. limiting the number of regulatory

Article	Proposed text	Comment
		EU website providing information on medicines or ensuring appropriate link). For example, access to the latest approved product information on a medicine should be easily accessible from any safety information. - its establishment and maintenance with sufficient human resources and use of identified electronic format for initial submission of the data by Industry. - that publication will not lead to duplication of work for the authority (e.g. preparation of public abstract and recommendations for product information based on a post-authorisation safety study report could be replaced by the publication of the Committee's assessment report after deletion of commercially confidential information). This would also be consistent with the EU access to document principle. See also EMEA comment 21 on key proposals for legislative change.
Article 101i(1)(g)		***Proposed change:*** The same terminology as in 101f(4)(b) should be used regarding European reference dates and frequency and dates of submissions.
Article 101j	Public list of product under intensive monitoring	***Proposed change:*** The proposal for a list of medicines under intensive monitoring should be further clarified. Publication of such a list is a good transparency initiative. It should however neither scare patients benefiting of the medicines nor being too exhaustive with any product for which there is safety consideration. Promotion of the reporting of all suspected adverse reactions for these products through warning in the product information is supported. Adding a patient adverse reaction reporting form to the PL for these products may introduce a bias of reporting (high reporting for these products and low reporting for the other products [in absence of form]). It is therefore questioned whether it would not be better to promote a single well-known tool for reporting adverse reactions (e.g. via a EU website redirecting the reporter to the relevant National reporting system).
Article 101k(3)		***Proposed change:*** To be revised to 'If the Agency with involvement of Members States identifies…." ***Justification:*** How is the Agency going to identify if an issue relates to more medicinal products if

Article	Proposed text	Comment
		they are nationally authorised?'
Article 101k(7)		***Proposed change:*** See also EMEA comments 3 and 23 on key proposals for legislative change. Regarding the announcement, when referring to paragraph 5, it should read **paragraph 6**.
Article 101k (10) (d)	Outcomes of Article 101k Opinions	***Proposed change:*** To revise to: "That the Member States and/or marketing authorisation holders need to …" ***Justification:*** Risk minimisation actions may also have to be implemented by MAHs.
Article 101l(l)		***Proposed change:*** Include an additional responsibility for the Agency: To give access to Eudravigilance data to the public and MAHs.
Article 101l(1)(g)		***Proposed change:*** Additional responsibility for the Agency: "(g) Establish and maintain an European network of centres of pharmacoepidemiology and pharmacovigilance in order to facilitate the conduct of post-authorisation safety studies." ***Justification:*** See also EMEA comment 8 on key proposals for legislative change.
Article 101l(2)(d)	Product identification for adverse reaction reports	***Proposed change:*** To revise to: The system shall have the ability to identify the medicinal products prescribed, dispensed and administered which are the subjects of an adverse reaction report. ***Justification:*** "Dispensed" should be extended by "dispensed or administered" because not all medicinal products are dispensed to the patients, some e.g. in hospital-setting, are

Article	Proposed text	Comment
		directly administered.
Article 101l(2)(e)	Responsibility for signal identification in EV	In this article, the EC allocates the responsibility for signal identification in EV to the MS if the MS is the competent authority and where no RMS exists. RMS responsibilities are allocated by Article 101l (5). In Article 101 (d) (2) of the EC proposal for the Directive, the responsibility for all products is allocated to the EMEA, in collaboration with MS. This may imply that ultimate responsibility lies with the EMEA, which would be contrary to Article 101l (2) (e). While sharing responsibilities within the EU regulatory network is appropriate, efficient and in fact crucial, it is proposed to the EC to consider clarifying ultimate responsibilities for signal identification. See also EMEA comment 16 on key proposals for legislative change.
Article 101l (4)	MAH responsibility for notifying new information	***Proposed change:*** To revise: … for notifying new information including clinical trial results and information on action in a third country in relation to the product under consideration by the marketing authorisation holder or by an authority and … ***Justification:*** Based on experience with MAHs not informing the competent authorities of new information such as regulatory action under consideration in a non-EU country, it is proposed to the EC to include this example specifically in the Directive.
Article 101l (4) (b)	MAH tasks	***Proposed change:*** To add wording from current Article 103 (c) of the Directive and revise to: "… ensure that any request from competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales and prescriptions and about the use of the medicinal product concerned." To add wording from current Article 103 (d) of the Directive and revise to: "… the provision to the competent authorities of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies and safety information from other studies." ***Justification:***

Article	Proposed text	Comment
		The MAH obligation to provide promptly information requested by the authorities, currently included in Article 103 (c) of the Directive seems to be missing. The current Article 103 (c) specifically mentions sales and prescription data. It should be considered that more data on the use of medicines may be needed, e.g. administration practices, frequent co-medication, potential for medication errors, use in sub-populations and co-morbidity, potential for harmful use outside the terms of the SPC and risk perception. Such data are needed for pharmacovigilance assessment as well as for tailoring communication of pharmacovigilance information to the public. The current Article 103 (d) requires the QPPV/MAH to provide to the competent authorities any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on PASS. The experts from the PhVWP/EMEA on PASS considered at their meeting in November 2007 to extend this requirement to safety information from other studies.
Article 101l (4) (e)	MAH tasks re RMPs	***Proposed change:*** To add at the end: "including monitoring of their outcome." ***Justification:*** The EC proposes in Article 1 (33) of the Directive that the RMP includes the assessment of its effectiveness. This implies MAH responsibilities in this respect. It is proposed to the EC to strengthen the MAH responsibilities accordingly in Article 101l (4) (e).
Article 101l(4)(e)		***Proposed change:*** To revise to: "Maintain and follow the risk management plan for the medicinal product including all risk minimisation measures and its outcome included in the risk management plan and the marketing authorisation." ***Justification:*** See also EMEA comment 6 on key proposals for legislative change. The EC proposes in Article 1 (33) of the Directive that the RMP includes the assessment of its effectiveness. This implies MAH responsibilities in this respect. In Article 101l (2) (f), the main responsibility is allocated to the MS, but still in collaboration with MAH. It is proposed to the EC to consider clarifying

Article	Proposed text	Comment
		responsibilities, possibly obliging MAHs to collect data and conduct studies on effectiveness as specified in the RMP and obliging MS to assess the information provided by MAHs in the light of their knowledge gained by their overall monitoring and surveillance activities.
Article 101l (4) (g)		***Proposed change:*** (1) New responsibility for MAHs: "Provide sales and utilisation data upon request". (2) New responsibility for MAHs: "Review processes and evaluate outcomes of communicating pharmacovigilance information to the public. The results should be communicated to the Competent Authorities". ***Justification:*** (1) The EC Legislative Proposal mentions sales and prescription data to be included in the PSUR, which is welcomed. It should be considered to broaden the wording because also other data on the use of medicines may be needed, e.g. administration practices, frequent co-medication, potential for medication errors, use in sub-populations and co-morbidity, potential for harmful use outside the terms of the SPC, risk perception. Such data are needed for pharmacovigilance assessment as well as for tailoring communication of pharmacovigilance information to the public and should be provided by the company on request. (2)The proposed requirement will provide a legal basis to a procedure currently included in Volume 9A. The results of such review are expected to identify further information needs of the public and to build-up a knowledge base for future advice on communication.
Article 101(l)(2)(c)	Supervisory authority for pharmacovigilance systems in the case of DCP and MRP as well as CAPs	***Proposed change:*** To revise to: "If the qualified person for pharmacovigilance for an authorised medicinal product resides in that Member State then the Member State shall act as the supervisory authority for pharmacovigilance inspections." ***Justification:*** The proposals for article 18(3) of Regulation (EC) No 726/2004 include establishing the supervisory authority for the pharmacovigilance system and QPPV for CAPs. In a similar way and to avoid redundant inspection the same approach should be taken for

Article	Proposed text	Comment
		MRPs and DCPs.
Article 101p (1)		***Proposed change:*** "The competent authority which granted the marketing authorisation may require a marketing authorisation holder to submit a risk management plan…" ***Justification:*** It is understood that the intention of this provision is to provide the legal basis for Competent Authorities to be able to request risk management systems for already authorised medicinal products, therefore no specific date would be required.
Article 111(1)(d)	Pharmacovigilance inspection	***Proposed change:*** (d) inspect the premises, records and documents, including the pharmacovigilance system master file, of marketing authorisation holders, or of any individuals or firms operating on their behalf including those located in third countries, for compliance with the activities described in the pharmacovigilance system master file and Title IX. The Agency and Member States, shall agree the guidelines and procedures for the establishment and operation of a risk-based pharmacovigilance inspection programme and shall agree and maintain the inspection programme itself. These guidelines and procedures shall be published by the Agency. ***Justification:*** See also EMEA comments 9 and 10 on key proposals for legislative change. The section on pharmacovigilance inspection has been clarified so that it includes sites in third countries and also those conducting pharmacovigilance "on behalf of" the MAH rather than simply "employed by" so that licensing partners, parent company etc are clearly included. A proposal for an inspection programme is made in order to ensure a cohesive and risk based process of inspection and avoid as much as possible redundant re-inspection or requests for assessment of the pharmacovigilance system master file during individual marketing authorisation applications.

Article	Proposed text	Comment
Article 111(8)	The Member States shall send all Pharmacovigilance inspection reports to the Agency.	***Proposed change:*** Replace the first sentence of the proposal for article 111(8) as follows: To be revised to: The inspection report referred to in article 111(3) shall include a record of the inspection and its outcome and the identity of the pharmacovigilance system master file(s) of the inspectee and these shall be entered by the Member States in a database managed by the Agency on behalf of the Community. If the outcome of the inspection as referred to in paragraph 1(d) is that the marketing authorisation holder does not comply with the pharmacovigilance system master file and Title IX, the Member State competent authority shall inform the other Member States, the Agency and the Commission. The Member State shall bring the deficiencies to the attention of the marketing authorisation holder and where appropriate shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties as referred to in Article 101n. ***Justification:*** If the Member States are to send all inspection reports to the EMEA there need to be provisions for this to occur in an organised and efficient way and to allow sharing of this information with the Member States and the Commission as well as the EMEA.

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Article	Proposed text	Comment
Article 23 (d)	Provision of information from PASS	***Proposed change:*** To revise to: "… providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly information concerning post-authorisation safety studies and safety information from other studies." ***Justification:*** The current Article 23 (d) requires the QPPV/MAH to provide to the competent authorities any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on PASS. The experts from the PhVWP/EMEA on PASS considered at their meeting in November 2007 to extend this requirement to safety information from other studies.