THE EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

SUBMISSION OF COMMENTS

TO THE EUROPEAN COMMISSION'S PUBLIC CONSULTATION ON PHARMACOVIGILANCE LEGISLATIVE PROPOSALS

COMMENTS FROM the EGA (European Generic medicines Association), rue d'Arlon 50, B-1000 Brussels

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GENERAL COMMENTS

General

The European Commission's legislative proposals have been well received and generally accepted by EGA members as they support the strategy to better protect public health by strengthening and rationalising EU Pharmacovigilance.

The EGA also appreciates the opportunity to contribute to this process by participating in discussions and in providing comments deriving from the internal EGA consultation process.

The following comments from the EGA are structured into sections and include general comments covering the key legislative proposals accompanied by detailed proposals on the EU legal texts themselves (in bold and underlined).

3.2.1 Fast, robust EU decision-making on safety issues by rationalising the existing EU referral procedures and reinforcing the committee structure

The EGA welcomes the introduction of a framework in which Commission decisions on referrals are considered binding for both Member States and Marketing Authorisation Holders alike. This will ensure that, for important safety issues, safety action is taken consistently in all Member States. This new approach will also provide a legal basis for adding important safety information such as contraindications, and special warnings to generic Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs), even if those new contraindications and warnings are related to indications which may still be covered by use patents on the molecule in certain Member States and as such are therefore not mentioned in the SmPC and PIL of the generic medicinal product concerned. Introducing new contraindications and warnings, for example, into SmPCs and leaflets is indeed part of minimising risk to the patients and should apply to all products concerned.

The EGA endorses the application of principles to ensure that respective changes to the contents of SmPCs will be accomplished through a fast and simplified variations process, such as for type 1a variations, without an additional assessment or approval process by the Competent Authorities.

The EGA also welcomes the approach to have the authorisation of products linked to the robustness of post-authorisation pharmacovigilance. It should, however, be made clear that requirements regarding robust post-authorisation pharmacovigilance should be adaptable and must take into consideration both product specificities and the knowledge already gathered on the product.

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3.2.2 Clarify/codify roles and responsibilities and codify standards for industry and regulators

The EGA highly welcomes a clear and binding codification of responsibilities and standards with consistent acknowledgement of results and decisions in the EU.

The current version of Volume 9A provides a very sound and comprehensive basis for a standardised approach to pharmacovigilance and for the definition of responsibilities for the different role-players involved in Pharmacovigilance operations. It must, however, be stressed that Volume 9A is a non-binding guideline and is often interpreted very differently by the different stakeholders in the EU.

The EGA strongly recommends that an amended version of Volume 9A (inclusive of the proposed principles applied in the consultative framework without adding opportunities for an increase in bureaucracy) serve as the legal basis of and/or paradigm for the proposed new codification.

The EGA proposes that the responsibilities for signal detection be clarified and defined in an updated Volume 9A. The proposed wording of Directive 2001/83/EC Article 101d point 2 attributes the task of signal detection to the Agency in collaboration with the Member States. The latter approach is fully supported by EGA since a much broader data pool is accessible to the Member States through Eudravigilance as compared to the rather limited data pools owned by generic medicines companies. Such an approach will ensure an even and consistent performance of signal detection activities regarding all authorised APIs. A new signal identified could then trigger requests for discussion or consultation on the signal between CAs and MAHs.

With regard to the concept of Good Vigilance Practices (GVP), clarification is needed whether GVP should be published as a guideline, as a regulation, or as part of the new directive. A directive would probably yield more or less pronounced Member State specific variations. The publication of GVP as part of a regulation would foster consistency throughout the EU, allowing no room for differences from one Member State to another, eg, regarding pharmacovigilance inspections. On the other hand, a guideline might go into much greater detail, which would certainly make it's inclusion in a directive or a regulation more difficult. The downside of a GVP guideline would be the lack of a requirement for it to be adhered to as strictly as a GVP regulation.

3.2.3 Simplify informing the authorities about the company pharmacovigilance system

The EGA welcomes the proposals which will immediately lead to a reduction in the number of variation submissions to be managed in the EU.

The EGA would like to propose an additional simplification to the process whereby the description of the PV system and the contact details of the European QP for PV, ie, the Pharmacovigilance System Master File, is submitted centrally to the Agency with the obligation of the MA holder to keep this documentation up to date.

The Agency can subsequently make the Pharmacovigilance System Master File available to all the authorities in the EEA by publishing this information on their secure safety portal/website. This is in line with the proposal made by the EC regarding Chapter 5 Communications, Article 101i 1(f), where it is stated that the Agency will publish a list of marketing authorisation holders and their qualified persons for Pharmacovigilance along with the Member States in which they reside.

The Application form for a new marketing authorisation should be amended to reflect this new approach by simply asking whether the applicant has submitted the current Pharmacovigilance System Master File including the current contact details of the EU QP PV person to the Agency. Such an approach would minimise the administrative burden both for the Marketing Authorisation Holders and the authorities whilst achieving and maintaining optimal transparency.

3.2.4. Rationalise risk management planning

The EGA supports the principles discussed in this section.

However, the EGA needs to caution against using terminology such as *'public health concern'* or *'safety concern'* without it being properly defined, especially in the context of newly approved medicinal products for which an RMP is required. Such strong wording might lead to confusion when used in the public domain.

The EGA would also like to see Risk Management viewed as a continuous process with a summary of the Risk Management Plan held in the public domain as is currently practiced via the EPARs. Such an approach would ensure harmonisation of the approach to risk management in relation to a molecule and would prevent duplication of effort for both legislators and marketing authorisation holders, especially at the time when it is legally possible to apply for a new marketing authorisation under article 10 of the Directive.

The EGA agrees with the principle to clarify the legal provisions in relation to risk management plans, which should only be required and submitted when they are needed. But when RMPs are required, they must be complied with fully within the timelines specified. For new applications, we also believe that the PSUR timetable should be included in the context and scope of risk management plans, and should become the tool through which risk assessment is performed, especially when a potential new signal is detected.

The EGA also proposes to further strengthen the risk/benefit based approach to the legislation by steering away from a time-dependant approach in submitting documentation as is the case with PSURs. PSURs cycles should be agreed based on the most recently assessed risk, and not on a pre-defined periodicity, which is the current practice, which has been proven not to add significant value in its current format, yet is probably responsible for consuming the greatest amount of resources both of industry and of regulators.

Furthermore, the terminology 'Risk Management System' and 'Risk Management Plan' should be more clearly defined.

3.2.5. Codify oversight of non-interventional safety studies

The EGA welcomes new legislation to clarify the criteria for non interventional studies involving safety investigations. Such new legislation should facilitate harmonisation between the Member States regarding the criteria to approve and assess safety studies.

3.2.6 Simplify and make proportional reporting of single serious adverse drug reaction (ADR) case reports.

The EGA supports all the principles discussed in this section. We support, in particular, that all EU domestic reports should be reported to Eudravigilance only. However, it should be clarified that domestic reports cover both serious and non-serious reports. Different reporting timelines should therefore be considered for serious and non-serious ADRs. We also suggest that consumer reports should be added to this obligation, and should probably be regarded as reportable in the same timeline as non-serious cases.

The EGA supports the proposal that the EMEA should be responsible for literature monitoring and reporting. However, the EGA would like to see clarified how MAHs will have access to this information. The EGA also suggests that literature case reports be available to MAHs as line-listings and in E2B compliant format available for direct exchange or download. The literature data should be as complete as possible and should cover all the worldwide scientific literature available from the relevant vendors.

As regards patient's reporting, Member States should be encouraged to take all appropriate measures to encourage doctors and other HCPs to report all, and to comment on or confirm any ADRs reported by patients/consumers. Patients should also be encouraged to provide details of his/her physician or other healthcare professional that would be able to confirm patient declarations. In order to avoid confusion in the patient's mind it would be more appropriate if all reports from patients go either to the MAH or to the National Competent Authority without distinction. It may be easier if reports from patients always went to the MAH first, as this would facilitate follow-up with the patients or the HCPs specified by the patients, thus reducing additional work for NCAs.

Furthermore, inclusion of patient adverse reaction reporting forms in the patient information leaflet (PIL) triggers several practical issues. The availability of only one ADR form will create problems in countries where the PIL must be available in three languages and when a patient experiences more than one ADR while using the medication from one particular package. While we welcome the use of the Internet, reporting by this means can only constitute one option, as there are age-related differences in computer literacy and not all patients have access to and knowledge of the Internet.

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3.2.7 Simplify and make proportional to risk periodic safety update report submission by industry (PSURs)

The EGA welcomes and strongly supports the proposal to simplify PSUR submissions and the intention to optimise the use of resources needed for preparing and assessing PSURs in a more rational way. The EGA disagrees, however, with the general idea that PSURs should no longer be written at all for older established products. Regular review in the current method of synchronised assessment of PSURs enables us to review the safety profile of a product from time to time and to add new contraindications or warnings to the Core Safety Profile which might, for example, be related to interactions with newly approved medicinal products. The timing, however, of the next PSUR in the cycle should be risk-based and determined in the harmonised assessment. This could result in the fact that, for example, for one product the next PSUR is required in a regular three-year cycle, and for another product only key data are needed (estimated exposure) to determine risk/benefit while for products such as vitamins, no PSUR is needed at all.

The proposal to submit PSURs exclusively to the Agency is very welcome as this will simplify logistics and reduce redundant filing activities, both with MAHs and at Member State level.

The EGA also agrees that the submission of listings as attachments to PSURs is no longer needed, considering that all case reports would already be available through Eudravigilance.

For new submissions, we strongly support the rationalisation of our resources and recommend that the periodicity of PSURs be linked to Risk Management Planning, as already discussed in section 3.2.4 - 'Rationalise risk management planning'. For older products the only 'published system' is the published next HBD for the next PSUR. It also means that the cycle could remain once every three years at the next assessment, or could be extended if there is no salient reason for a three-year cycle.

3.2.8 Strengthen medicines safety transparency and communication

The EGA agrees that the current legislation needs to be updated to prevent opportunities for misunderstanding and miscommunication at different levels in the community to the confusion of the general public.

It is important to ensure, through the new legislative framework, that the new Pharmacovigilance Committee is empowered not only to coordinate, but also to ensure that the Member States communicate a harmonised message.

We would also welcome further clarification regarding the development of an EU pharmaceuticals dictionary. It would, however, have to be clarified in terms of intent, ie, whether it refers to the EudraPharm or to the EVMPD database?

3.2.9 Clearer safety warning in product information to improve the safety use of medicines.

The EGA supports all methods and means to improve the safe and rational use of medicines. We do, however, have concerns that adding a new section on 'key safety information' to the Summary of Product Characteristics and to the Patient Information Leaflet will diminish the focus of the various sections containing other important information.

It is our understanding that this 'key safety information' section should be limited to only a few selected key elements. It is therefore our concern that, by emphasising 'key' safety information, other safety information may be regarded as not so important and will therefore not be considered during the treatment of patients. The EGA also believes that the approach might augment the risk of increasing non-compliance to prescribed medicine by patients/users as they might consider taking the product as more risky than leaving their underlying disease untreated. This probably calls for considering a new approach to patient empowerment. Furthermore, the potential impact on companies' liability must be discussed if certain safety information is highlighted while other safety information is not.

The EGA suggests that the existing sections (of the Summary of Product Characteristics and the Patient Information Leaflet) concerning adverse reactions and warnings should be discussed in the context of the current ongoing review of the Guideline on SmPCs.

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SPECIFIC COMMENTS ON THE LEGISLATIVE TEXT		
GUIDELINE SECTION TITLE		
Line number + paragraph number	**Rationale**	**Proposed change (if applicable)**
Directive 2001/83/EC Article 1(15)	At the moment there is no established definition for 'safety hazard', a term which appears to be confusing to the general public. We propose changing 'safety hazard' into 'a new safety issue".	.....characterising or quantifying a ~~safety hazard~~ **new safety issue** or confirming the safety profile of the medicinal product.
Directive 2001/83/EC Article 8(3)(ia)	When the Agency publishes the Pharmacovigilance System Master File on their safety portal/website as proposed by the EGA, a statement to the effect that the PV System Master File has been submitted should be sufficient	~~A detailed description of the pharmacovigilance and where appropriate, of the risk-management system the applicant will introduce.~~ **A statement that the current Pharmacovigilance System Master File, including the name and contact details of the European Qualified Person for Pharmacovigilance has been submitted to, or is already available at, the Agency**
Directive 2001/83/EC Article 8 (3)(iaa)	The EGA proposes new text to align this new article with the EGA's recommendations made to section 3.2.4. 'Rationalise risk management planning'.	If applicable, a detailed description of the ~~pharmacovigilance and, where appropriate, of the~~ risk-management system which the applicant will introduce. **This~~e~~** risk management system shall be proportionate to the identified and potential risks taking into consideration the **current** information available on the medicinal product **at the time and summary of the current agreed system will be maintained in the public domain.**
Directive 2001/83/EC Article 8(3) (n)	In line with the EGA proposal, proof that the applicant has the services of a QP responsible for PhV should be centrally available on the Agency's safety portal/website. Therefore, there is no need to provide proof of this at the time of application.	~~Proof that the applicant has the service of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.~~
Directive 2001/83/EC Article 21, point 1, 2nd paragraph	In "3.2.4 Impact" it is specified in paragraph 2 that Risk Management Plans are only to be submitted when they are needed.	The risk management system shall be annexed to the marketing authorisation, **if applicable**.

Directive 2001/83/EC Article 22	The EGA suggests that the content of the Risk Management Plan should be discussed with the applicant before the final decision is made (at the time of list of questions during the procedure). We would therefore like to keep the phrase "following consultation with the applicant" in the Directive.	**Following consultation with the applicant,** a marketing authorisation may be granted subject to the following conditions……
Directive 2001/83/EC Article 23	Under the EGA's proposal, the applicant will have submitted a copy of the pharmacovigilance system master file to the Agency, thus eliminating the need for the competent authorities to request a copy. The last line of this draft article can be deleted.	… ~~The competent authorities may at any time ask the holder of he marketing authorisation to submit a copy of the pharmacovigilance systems master file.~~
Directive 2001/83/EC Article 101a	As the reporting by healthcare professionals (HCPs) is one of the weakest points in Pharmacovigilance throughout the EU, the EGA welcomes the encouragement to Member States to take all appropriate measures to urge doctors and other HCPs to report suspected ADRs. Furthermore, the EGA fully supports that any medicinal product prescribed and dispensed in the EU which is the subject of an adverse reaction report should be identifiable. The EGA is, however, concerned that the proposed Article 101a encourages Member States to impose country specific labelling or other reporting requirements on biological medicinal products which will lead to non-harmonised methods of collecting information and identification of biological medicinal products. One of the aims of the new EC legislative proposals is to achieve a harmonised and consistent approach to pharmacovigilance. The wording of the proposed Article 101a, however, has the potential to introduce new disharmony, which must be avoided. Article 101a, or a separate article, should make clear, as in the recently updated Volume 9a, that an adverse reaction report for any biological medicinal product should always include the full name of the medicinal product as approved by the Competent Authority, the name of the Marketing Authorisation Holder, the name of the active substance, and the batch number.	The Member States may impose specific requirements on doctors and other health care professionals in respect of the reporting of suspected serious ~~or unexpected~~ adverse reactions. ~~Through the methods of collecting information and where necessary through the follow up of adverse reaction reports~~, The Member States shall ensure that any biological product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable. **This implies that an adverse reaction report for any biological medicinal product should always include the full name of the medicinal product as approved by the competent authority, the marketing authorisation holder, the name of the active substance and the batch number. Where information is missing, Member States should ensure that reports are followed up for completion.**

	The 2nd paragraph of Art. 101a also mentions unexpected adverse reactions. In order to maintain consistency throughout the new legislation, 'unexpected adverse reaction' should be deleted as the EC proposal has deleted Article 1(13) of Directive 2001/83/EC.	
Directive 2001/83/EC Article 101d Point 2	The Agency will monitor Eudravigilance for signals of active substances. Every signal needs to be evaluated to see whether a new risk has been identified. This discussion should take place together with the Member States and all marketing authorisation holders should be able to take part in the discussion.	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 new or changing risks of medicinal products~~ of active substances authorised in the Community. In the event a ~~change~~ **signal** is being detected, the Agency shall ~~inform~~ **evaluate together with** the marketing authorisation holders and the Member States and **will inform** the Commission of the ~~findings~~ **final decision made.**
Directive 2001/83/EC Article 101d point 3	We suggest that only predefined parts of the individual adverse reaction reports be made available to the public. As the access policy to Eudravigilance may vary over time, this should be reflected in the legal text.	3. **Predefined parts** of ~~the~~ individual **case safety** ~~adverse reaction~~ reports, **as decided by the access policy**, held on the ……
Directive 2001/83/EC Article 101e point 1	We propose that subparagraphs a and b be simplified and merged.	**Reports where the Patient or the Healthcare Professional has not excluded a causal relationship between the event and the medicinal product or has not made any statement on the suspected causal relationship..**
Directive 2001/83/EC Article 101e point 2	We fully support the submission of all ICSRs to the Eudravigilance database. We do, however, believe that non-serious reports do not need to be expedited and can have a 60-day timeline. By giving them a flag in the E2B report, they can be excluded from the compliance calculations on the 15-day reporting of serious reports.	Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15-days following the receipt of the report, all serious adverse reactions that occur **in** ~~the Community~~ **and** ~~all serious adverse reactions that occur~~ **outside** the Community. **Non serious adverse reactions that occur in the Community should be reported within 60 days following the receipt of the report.** These reports are ~~should be made~~ available to the Member States through Eudravigilance.
Directive 2001/83/EC Article 101e point 3	To minimise duplicate reporting, Member States should avoid sending reports to Marketing Authorisation Holders received other than through spontaneous sources reported directly to the Member State.	….. Member States shall submit electronically to Eudravigilance and to the marketing authorisation holders all of these reports which meet the notification criteria in accordance with the guidelines

		referred to in Article 101b and **which are reported directly to the Members States via initial reporters (health care professionals or patients)**
Directive 2001/83/EC Article 101e point 5	To be compliant with the current requirements for literature reporting, worldwide sources should be reviewed for relevant case reports on key ingredients registered. Industry should be able to download line listings and case reports directly from the database in E2B format.	The agency shall monitor **worldwide** medical literature for reports of adverse reactions to **active ingredients** ~~medicinal products~~ for human use authorised or registered in the Community. It shall publish the list of publications subject to this monitoring and it shall enter into Eudravigilance relevant information from the identified literature. **Respective case files are available to MAH for download as line listings and E2B reports.**
Directive 2001/83/EC Article 101f point 2	Activities in relation to PSURs should be risk-based rather than time based.	c) In the absence of specification pursuant to either point a) or b) above ***within 60 days of request***. ~~immediately upon request or at least every six months after authorisation and until the placing on the market. Thereafter, periodic safety update reports shall be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three -yearly intervals, or immediately upon request.~~
Directive 2001/83/EC Article 101f point 3	The EGA welcomes and supports the proposal to simplify PSUR submission and the intention to avoid unnecessary reports as described above under 3.2.7. But a regular review in the current way of synchronised assessment of PSURs enables us to review the safety profile of a product from time to time and to add new contraindications or warnings to the Core Safety Profile which might, for example, be related to interactions with newly approved medicinal products. The timing, however, of the next PSUR in the cycle should be risk-based and determined during the harmonised assessment.	Delete Article 10, 10a of point 3
Directive 2001/83/EC Article 101f point 4(a)	This sentence could potentially be misinterpreted (Why should the Committee on Pharmacovigilance only have the right to determine the frequency for **some** products? Which are these?)	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.

	If the first authorisation is not known, it cannot be set as the reference.	For the purposes of this provision, the European reference date for products containing the same active substance shall be the date of the first authorisation in the Community of a medicinal product containing that substance. ~~The same applies~~ If the date of the first authorisation in the Community cannot be determined, **the Committee on Pharmacovigilance will define a reference date.**
Directive 2001/83/EC Article 101f point 4(b)	The huge effort that has already been made to prepare the list on Harmonised Birthdays and related Data Look Points should be recognised. These dates should be taken as the basis for the list described under this article, especially since companies have already been harmonising their submissions according to these dates since Nov 2006.	the Committee shall draw up and maintain a list of European reference dates and frequency and dates of submission fixed in accordance with point (a) above , which shall be made public by the Agency via the European medicines safety web-portal referred to in Article 10 1i. **The existing list of Harmonised Birthdays at the time of entry into force of this directive and the related Data Lock Points shall form the basis for this list.**
Directive 2001/83/EC Article 101f point 4(c)	The intention is to harmonise PSUR submissions in order to have all information available at a certain point in time. To now give MAHs the option to negotiate the harmonisation of reference dates will again become very difficult and the harmonisation already achieved with the HBDs will be lost. It should not be possible to negotiate reference dates once they have been published on the web/portal.	marketing authorisation holders for medicinal products requiring periodic safety update reports may submit requests to the Committee on Pharmacovigilance to change the ~~European reference date or~~ frequency of submissions ~~schedule~~ for periodic safety update reports. The Committee on Pharmacovigilance shall have the authority to change the reference date and the submission schedule even when these are conditions of the marketing authorisation and the schedule shall be made public by the Agency via the European medicines safety web -portal referred to in Article 101i.
Directive 2001/83/EC Article 101f point 4 (d)	We feel the deadlines should be defined.	~~by way of derogation of paragraph 3 above,~~ the Committee may request a periodic safety update report for products ~~referred to in that paragraph~~ in case of a suspected pharmacovigilance risk. The **committee should define the period under review and the MAHs shall be given at least 60 days from Data Lock Point to submit the report.**
Directive 2001/83/EC Article 101f	It would seem better to set day 0 for the deadline of the assessment report as the day when the last PSUR should be	the Member State or rapporteur responsible for the periodic safety update report assessment shall produce an

point 4(f)	submitted (60 days after the requested Data Lock Point); this enables the assessor to consider all information available through all submitted PSURs and will harmonise the deadlines for the MAHs to respond to the assessment report.	assessment report within 90 days of ~~receipt~~ **the latest possible submission date (60 days after the requested Data Lock Point)** of the periodic safety update report and this shall be sent to the marketing authorisation holder and the Committee on Pharmacovigilance. Within 30 days of receiving the assessment the marketing authorisation holder may submit comments on it to the Member State or rapporteur and the Committee on Pharmacovigilance.
Directive 2001/83/EC Article 101f point 4(i)	The Competent Authorities should provide translations in the local language within 90 days of the final decision on the core safety profile and other parts of the SPC, as applicable. 90 days after that, MAHs should submit the updated SPCs and PILs through a fast review process as for a type 1a variation.	Competent authorities **shall provide translated SPC and PIL changes in their local language(s) within 90 days** and marketing authorisation holders shall **submit updated SPC and PIL texts within 90 days after that date through a simplified type 1 variation**. ~~take account of the recommendations for the product information~~.
Directive 2001/83/EC Article 101i point 1(f)	For reasons of safety, names of qualified persons should not be in the public domain. A list with the names and contact details of marketing authorisation holder qualified persons for Pharmacovigilance, the Member State in which they reside, and the Pharmacovigilance System Master File of the marketing authorisation holders should be accessible to the authorities of the Member States.	A list of marketing authorisation holder **contact details** ~~qualified persons~~ for pharmacovigilance and the Member State in which they reside.
Directive 2001/83/EC Article 101i point 6	We propose the addition of personal details.	….. any information of a commercially **or personally** confidential nature shall be deleted……
Directive 2001/83/EC Article 101k point 1	We suggest that the marketing authorisation holder should be informed of decisions taken at the same time as the other Member States.	…. Shall notify the other Member States, **the marketing authorisation holders**, the agency…..
Directive 2001/83/EC Article 101k point 5	We suggest informing the marketing authorisation holder on all scientific information.	…. Shall make available to the Agency **and the marketing authorisation holders** all scientific information….
Directive 2001/83/EC Article 101l	To maintain the current risk management system in the public domain, add the proposed wording in point (g):	**(g) Maintain the latest risk management system on the Agency website**

Directive 2001/83/EC Article 101l 4(a) line 3	The wording "the competent authority" is ambiguous. It should be clarified whether this refers to the CA of the QPPV's country of residence or the CA of the country where the MAH resides.	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.
Article 101l point 4 f)	Having internal audit reports of the MAH available in the description of the pharmacoviglance master files would generate either a very limited number of reports or modified standards of auditing. We propose the wording be changed so that the MAH ensures that GVP is performed.	Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices and **ensure preparation of and follow up on a corrective action plan according to the audit results.** ~~place a report of the audit on the pharmacovigilance system master file.~~
Directive 2001/83/EC Article 101p	To ensure the optimal use of resources by both competent authorities and marketing authorisation holders, we suggest an addition to point 3 of the proposed article:	3. On the basis of explanations submitted by the marketing authorisation holder,, the competent authority may withdraw the requirement or issue a final requirement, **which should be agreed by all competent authorities in which a marketing authorisation is sought, or in the case of a dispute, agreed by the Committee on Pharmacovigilance**.
Directive 2001/83/EC Article 111 point 3	We think it is appropriate, when the MAH is able to comment on the report, that this comment should also be circulated amongst the other Member States. We suggest adding this approach to the Directive.	…with the requirements laid down in Article 101a to 101p. **The marketing authorisation holder will be able to comment on the report.** The content of the report **as well as the comment of the marketing authorisation holder** shall be communicated…
Directive 2001/83/EC Article 111 point 8	Nothing is specified within this new paragraph regarding the issuance of a MAH-comment to the audit report prepared by the authority. The reference in the last line needs to be corrected. It should refer to Article 101o	**The CA 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** and to the Agency. If the outcome of… Proportionate and dissuasive penalties as referred to in Article 101**o**~~f~~.

Regulation (EC) No 726/2004 Article 57(2) point 2	The new additions to the Regulation need further clarification. The product information forms part of the regulatory files for submission and therefore is already submitted to the Member States when a product is authorised.	Delete the additions