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agencia española de medicamentos y productos sanitarios

DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS SANITARIOS

UAP/INTE/LFG

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Madrid, 19 February 2008

Re: *Public consultation on legislative proposals: Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance*

Dear Mr. Arlett,

Please find enclosed the Spanish comments on the Public Consultation on legislative proposals: Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance.

Yours sincerely,

agencia española de medicamentos y productos sanitarios
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DIRECCIÓN DE LA AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

Strategy to Better protect Public Health by Strengthening and Rationalising EU Pharmacovigilance

Public Consultation on Legislative Proposals

Comments from Spain

Spanish Agency for Medicines and Healthcare Products

January 2008

INTRODUCTION

Pharmacovigilance rules in the EU are included in the Community Code on medicinal products for human use (Directive 2001/83/EC as amended), in a regulation of the European Parliament and the Council for centrally authorised products (Regulation (EC) No 726/2004), in a Commission Regulation (Regulation (EC) No 540/95) and in Commission guidance (Volume 9A of Eudralex2). Although the legislation was updated in 2004 the changes to the pharmacovigilance provisions were relatively minor.

The EC launched the public consultation of their proposals for amending the pharmaceutical legislation to strengthen pharmacovigilance on 5 December 2007.

The Spanish Agency for Medicines and Healthcare Products endorses the overall aim of the European Commission proposal. The need to strengthen the legal framework and rationalising the EU Pharmacovigilance is recognised.

Herewith, comments from the Spanish Agency for Medicines and Healthcare Products (AEMPS) on the proposals for amending the legislation on Pharmacovigilance in the EU including specific alternative proposals are presented.

Comments are ordered according to the subsections included in section 3.2 of the Public Consultation document (Key proposals for legislative change) and expressed directly on the detailed proposals to change the EU legal texts presented in section 4 of the Public Consultation document.

> Drafting Code: Legal text as proposed in the Consultation Document is presented in *italics*.. Where it is proposed to delete existing text the deleted text is presented as ~~*strikethrough*~~. Where new text is proposed this text is *underlined*.

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

a) Within the European Medicines Agency (EMEA), establish a committee (to replace the existing Pharmacovigilance Working Party)

The proposal to establish a Committee on Pharmacovigilance is endorsed. Nevertheless, the functioning and responsibilities of the new Committee should provide added value to the current system. Duplicated evaluation procedures of the safety issues in the Committee on Pharmacovigilance and in the CHMP should be avoided due to the increased workload this implies. On the other hand, it should be ensured that decisions pre- and post approval are consistent and that there is no separation between efficacy and safety issues as matter of different committees, without compromising a robust procedure for benefit-risk assessment of centrally authorised products (CAP).

b) Rationalise the referral procedures

Spain supports the rationalisation of existing EU Referral procedures. In relation to the new referral procedure defined in Directive 2001/83/EC Article 101k, the following changes are proposed:

Directive 2001/83/EC Article 101k

- It should be clarified that the procedure should only be triggered in case the applicable condition (from a- to f-) arise on the basis of safety concerns

> ***Article 101k 1.*** *A Member State shall notify the other Member States, the Agency and the Commission and shall thereby initiate the procedure of this article where, on the basis of safety concerns:*

- Regular public hearings will involve significant use of regulatory resources with diversion of activities away from other safety issues impacting on public health. The added value of public hearings for every Referral is not perceived and therefore is not endorsed. Other options should be closely explored as a decision on a case by case basis. Therefore **Article 101k 7**, should be modified accordingly.

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

For the Member State competent authorities, EMEA (including its committees), Commission and Marketing Authorisation Holders including their qualified person, clarify and codify their tasks and responsibilities in the legislation. "..establish the concept and scope of Good Vigilance Practices (GVP)"

Directive 2001/83/EC Article 1011 2 f) (Responsabilities for Member States)

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Relevant information to monitor the outcome of risk minimization measures needs to be obtained in the clinical setting or by means of drug utilization data which are inherently in control of member states. Spain proposes that this responsibility of the Member States should be applicable to all authorised products, but taking into account the need for coordination by the Agency of this task at the European level.

> ***Article 101l 2 f**: In collaboration with the marketing authorisation holders and the Agency, monitor the outcome of risk minimization measures relating to ~~nationally~~ all authorised products.*

Article 101 L 1 d should also be modified accordingly

Directive 2001/83/EC Article 101 l 4) (Responsabilities for the MAH)

The following amendments are proposed in this article in order to be comprehensive:

> *e) Maintain and follow the risk management system for the medicinal product including all post-authorisation safety studies and risk minimization measures included in the risk management ~~system~~ plan and the marketing authorisation.*
>
> *f) Perform regular audit of its pharmacovigilance tasks including its performance of Good Pharmacovigilance Practices and place a report of the audit on the pharmacovigilance system master file.*

3.2.3. Simplify informing the authorities about the company pharmacovigilance system

The creation of pharmacovigilance system master files is supported.

3.2.4. Rationalise risk management planning

A more clear legal basis for risk management plans and for the oversight of the fulfilment of the conditions (laying down deadlines in the marketing authorisation) is supported.

Directive 2001/83/EC Article 1(33) (Definitions): Risk management system:

The risk management system is defined to be product specific. In that case there will be no difference with the risk management plan and the latter term is preferable. If there are reasons to retain both terms it is suggested that risk management system is defined as company-specific. In addition, the current definition of risk management system (plan) does not capture its proactive nature which is the major contribution of the new concept. Therefore, Spain proposes to reword Article 1(33) as follows:

> *Risk management ~~system~~ plan: a set of pharmacovigilance activities and interventions designed to proactively identify, characterise, prevent or minimise risks relating to a specific medicinal product, including the assessment of the effectiveness of those interventions.*

Directive 2001/83/EC Article 22

The possibility to impose certain conditions in the marketing authorisation (included in the risk management plan) at the time of the authorisation for new products (Article 22) should also be extended

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to products already in the market (including deadlines for the fulfilment of the conditions). Therefore, it is proposed to amend Article 22 included in the Commission Consultation Document as follows:

> *1. A marketing authorisation may be granted subject to the following conditions, included in the risk management ~~system~~ plan:*
>
> > *(a) the requirement to conduct post-authorisation safety studies , or,*
> >
> > *(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, including the requirement to implement additional risk minimization measures or the evaluation of their effectiveness*
>
> *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.*
>
> *2. Conditions detailed in paragraph 1 may also be imposed once the marketing authorisation has been granted when the assessment of new data raises concerns about the risk affecting the risk-benefit balance of an authorised medicinal product.*

It should be stated that a risk management plan needs to be updated and that the periodicity for that should take into account the periodicity of periodic safety update reports unless otherwise stated by competent authorities.

In case of not fulfilment, the Article 22 establishes the possibility of revoking the marketing authorisation but other dissuasive measures could also be adopted (e.g. the prohibition to supply the product to new patients).

Directive 2001/83/EC Article 101 p 2

It is proposed, in order to simplify the procedure, to reword the article as follows:

> *2. The competent authority shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within ~~a time limit which it shall specify, if the marketing authorisation holder requests this within~~ 30 -days of receipt of the requirement. In exceptional circumstances, this time may be extended.*

3.2.5. Codify oversight of non-interventional safety studies

The oversight of post-authorisation safety studies by competent authorities, which gives support to the liaison between marketing authorisation holders and competent authorities laid down in Volume 9A is supported. A legal basis to enforce the conduct of post-authorisation safety studies is supported.

Directive 2001/83/EC Article 1(15) (Definitions): post-authorisation safety study

The new definition for post-authorisation safety studies is supported although it should be completed: A post-authorisation safety study may also have the aim of evaluating the effectiveness of a risk minimisation measure and this should be included in the definition:

Post-authorisation safety study: A pharmacoepidemiological study or a clinical trial with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product, or evaluating the effectiveness of a risk minimization measure

In addition, as it is explained later a definition for post-authorisation studies should be provided in the Directive.

Directive 2001/20/EC / Directive 2001/83/EC

Definition of non-interventional trials

Most post-authorisation safety studies concern "non-interventional studies". The definition of "non-interventional trials" in the Directive 2001/20/EC is quite well in accordance with retrospective observational studies but it creates a lot of confusion to the sponsors and researchers of prospective observational studies because many of them may be classified as clinical trials having a tremendous negative impact on the performance of post-authorisation safety studies. It is proposed to take advantage of this legislative initiative and modify the definition of non-interventional trial in order to accommodate all observational studies. In particular, the part of the definition which reads "No additional diagnostic or monitoring procedure shall be applied to the patients" should be deleted. Therefore, Spain proposes that this definition should be amended in EU legislation as follows:

*'**Non-interventional ~~trial~~ study**': a study performed with an authorised medicinal product in which ~~where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation.~~ the assignment of the patient to a particular therapeutic strategy is not decided in advance by a ~~trial~~ study protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. ~~No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.~~*

Directive 2001/83/EC Article 101g 2

It is proposed, in order to simplify the procedure, to reword the article as follows:

2. The competent authority shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within ~~a time limit which it shall specify, if the marketing authorisation holder requests this within~~ 30 -days of receipt of the written requirement. In exceptional circumstances, this time may be extended.

Directive 2001/83/EC Article 101h

Prohibition of post-authorisation studies on grounds of their promotional nature

The legal basis for prohibiting the conduct of post-authorisation safety studies (PASS) where the act of conducting promotes the use of a medicinal product is supported.

The legal initiative to forbid those PASS where the act of conducting them promotes the use of a medicinal product should be extended to all post-authorisation studies. To do that, the Article 101h should be divided into two points, the first concerning all post-authorisation studies and the second only to PASS. In order to be operative the oversight of post-authorisation studies should be performed at national level. A general statement in the EU legislation such as "Member States may impose specific

obligations to the sponsors of post-authorisation studies in order to control the appropriate use of these studies" could be enough. A definition for post-authorisation studies should be provided in the Directive.

Approval of protocols for post-authorisation safety studies by competent authorities

The Article 101h is too detailed in the procedures. It is preferable that the Directive includes a clear statement concerning the obligation of the marketing authorisation holders to report the study protocols leaving the procedures to the guidelines (Volume 9A). Additionally, a distinction should be made between those post-authorisation safety studies that are required by the competent authorities and/or included in the risk management plan and those performed at the marketing authorisation holder's initiative. Only the former should have a formal approval by the competent authorities (or the Pharmacovigilance Committee), in line with what it is already stated in the Volume 9A.

Directive 2001/83/EC (to include where appropiate)

Legal support to the public funding of independent studies

A general statement providing legal support to the public funding of independent studies on urgent safety issues is missing.

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

a) Eudravigilance (EV)

The current EudraVigilance database does not meet the needs of national competent authorities for signal detection. There are a lot of problems with the current database- ATC code is missing, problems to identify active substances with a consistent codification system, only pre-defined queries are available, duplicate detection is not satisfactory. The database should be fully validated and quality management procedures need to be evaluated.

Directive 2001/83/EC Article 101 d

- It should be clearly stated in the legislation that the role of assessing and prioritizing signal detection in Eudravigilance corresponds to the Committee on Pharmacovigilance. Therefore Spain proposes that **Article 101 d 2** should be reworded as follows:

> *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 Committee on Pharmacovigilance ~~marketing authorisation holder, the Member States and the Commission of these findings~~ .*

- The provision for making accessible to the public information in Eudravigilance is already stated in Directive 2001/83/EC Article 102. Spain's opinion is that this possibility should not increase unnecessarily the workload and the bureaucracy in European pharmacovigilance. Therefore Spain proposes that **Article 101 d 3** should be reworded as follows:

3. Information on Individual adverse reaction reports held on the Eudravigilance database may be accessible to ~~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.~~

b) Simpler ADR reporting to reduce burden and free up resource

Directive 2001/83/EC Article 101 e 1. (adverse reactions recorded by MAHs)

The proposal from the EC in relation to the reported cases recorded by the MAH establish some differences depending on considerations on the causal relationship between the event and medicinal products but does not make any difference between cases reported from healthcare professionals or directly from patients. Nevertheless, this difference is crucial. While healthcare professionals reports are triggered because an adverse reaction is suspected (therefore the suspicion of a causal relationship is inherent to the act of reporting) this is not the case in patient reports which are not later medically confirmed by means of a suspected diagnosis of an adverse reaction. Therefore Spain proposes that **Article 101 e 1** should be reworded as follows:

1. Marketing authorisation holders shall record all adverse reactions in the Community or in third countries which are brought to their attention. 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) All reports from ~~where the Patient or the~~ Healthcare Professionals ~~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 from ~~where the~~ Patients confirmed by ~~or~~ the Healthcare Professional ~~has not made any statement on the suspected causal relationship or has stated~~

~~that the causal relationship is unknown but~~ or when the temporal relationship between the exposure to the medicinal product and the adverse reaction means that a causal relationship can not be excluded.

Directive 2001/83/EC Article 101 e 2. (adverse reactions submitted by MAHs)

It should be clear in the legislation that reports registered by a MAH should be first come to the national competent authority. Marketing authorisation holders should continue to report to the national competent authorities where the adverse reaction occurred in order that national competent authorities hold complete adverse reaction datasets for their own country for the purposes of country-specific signal detection, and control of duplicate reports by direct information from the primary source of the individual case safety report data.

In addition, a quality assurance of reports is performed by many national competent authorities and Regional Pharmacovigilance Centres in those MS where are established. This can include causality assessment, requesting additional documentation on the case, analysing listedness, control of duplicate reports, etc. This quality assurance of reports obtained from the primary source of the cases in the clinical setting made by national competent authorities constitutes the basis of the final quality of the EudraVigilance database.

By the other side, direct submission to Eudravigilance of adverse reactions that occur outside the Community is endorsed.

Therefore Spain proposes that **Article 101 e 2** should be reworded as follows:

> *2. Marketing authorisation holders shall submit electronically to Competent Authorities in member states ~~Eudravigilance~~, no later than 15 -days following the receipt of the report, all adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community.*
>
> *These reports of adverse reactions that occur outside the Community will be made available to the Member State through Eudravigilance.*

Directive 2001/83/EC Article 101 e 4 (Web-based reporting by healthcare professionals and patients into EudraVigilance)

It is not clear from the Public Consultation document if these reports would first come to the national competent authority. The national competent authority link with local healthcare professionals and patients plays a vital part in the effectiveness of national reporting schemes and to remove this link with direct reporting to EudraVigilance would seriously undermine national schemes which are the basis of the data collected in EudraVigilance. Therefore Spain proposes to delete this paragraph:

> ~~*4. By / (5 years after the entry into force of this directive), the Agency, in collaboration with the Member States shall make available web based structured reporting forms for European healthcare professionals and patients to facilitate electronic reporting of adverse reactions and submission to Eudravigilance.*~~

c) Regarding medication errors the definition of adverse drug reaction would be clarified as would the reporting rules

Definitions and reporting rules for adverse reactions caused by medication errors are endorsed. The following comments and proposals on the legal text are presented below:

Directive 2001/83/EC Article 1 (Definitions)

The new proposed definition for "adverse reaction" in **article 1 (11)** is endorsed. Nevertheless, Spain proposes to maintain the definition for "abuse of medicinal products" as it is in **Article 1 (16)** of current Directive. This is needed to clarify that while "abuse" refers to intentional use and adverse reaction excludes intentional responses to a medicinal product, it is still possible that a patient who meets the definition of "abuse", might suffer a noxious and unintended response to that medicinal product and therefore an "adverse reaction".

Directive 2001/83/EC Article 101 e 3 (medication errors causing adverse reactions)

The reporting of these cases could potentially imply legal implication and liability for the reporters. This is supported in legislation in some Member States. Therefore, Spain proposes to add the following text in the 3rd paragraph of **Article 101 e 3:**

> *The Member States shall ensure that reports of medication errors brought to their attention in the framework of adverse reaction reporting for medicinal products are made available to any*

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national competent authorities for patient safety within that Member State. They shall also ensure that the national competent authorities for medicinal products are notified of any adverse reactions brought to the attention of national competent authorities for patient safety. A special procedure for reporting of medication errors leading to adverse reactions may be established in order to assure confidentiality of primary source identity.

c) Establish a European list of medicines under intensive monitoring

Directive 2001/83/EC Article 101 j

The general idea of a list of medicinal products for which pharmacovigilance is more active is supported. Nevertheless, Spain proposes that the term "intensive monitoring" as well as the proposed way for selection of products to be included in the list should be revised.

Spain is of the opinion that the concept would rather be an approach used for all new products. Therefore, it is proposed to modify the concept including a change in the term "intensive monitoring list". It's also proposed to apply the concept to all new products containing new active substances and to use instead the term "list of medicinal products with new active substances under surveillance". The products would be included in the list until the renewal of the authorisation has been granted.

Directive 2001/83/EC Article 54 o

Spain does not support the inclusion of any statement in the packaging regarding the need for reporting adverse reactions. Therefore Spain proposes that this paragraph should be deleted.

Directive 2001/83/EC Article 59 ba

Spain considers that the suspected adverse reactions should not be directly reported by the patients to the MAH and accordingly this should not be stated on the package leaflet.

d) Make clear the legal basis for patients to report suspected adverse drug reactions

Although Spain considers patient reports as a further valuable source of safety information, some concerns about the value of patient reporting are not solved , particularly about the involved resources.

The proposal for adverse reactions for intensively monitored medicines to be sent to marketing authorisation holders is not supported. It sends the wrong signal to reporters as to where the responsibility for medicines safety lies; there may be language and cultural issues which would impede reporting and patients in particular may be likely to be less willing to report to MAH. Accordingly this should not be stated on the package leaflet.

The provisions in **Article 101 e, 3**, second paragraph are not endorsed: "To facilitate the reporting of suspected adverse reactions by healthcare professionals and patients each Member State shall accept reports of adverse reactions via their websites which shall be linked to the European medicines safety web-portal referred to in Article 101 I".

It would very confusing to the patient to have to use different channels for ADR reporting. Furthermore the roles of the regulators and the MAHs could be mixed.

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

a) Link PSURs to risk management planning and therefore the knowledge about the safety of the product.

Directive 2001/83/EC Article 101f

- Spain supports the concept that periodic safety update reports (PSURs) will be focused on data relevant to the benefits and risks of the medicinal product. Nevertheless the provision to remove line listing of individual case reports already in Eudravigilance specified in **Article 101f 1** is not endorsed because:

- PSUR contents are internationally harmonized documents included in ICH Guidelines. Therefore, any proposal to remove information such as the line listings of individual case safety reports (ICSR) should be previously agreed by ICH members.
- At the moment there is no way to ensure that information on ICSRs related to any specific medicinal product in Eudravigilance can be correctly retrieved, classified and duplicate cases fully removed, taking into account the different sources a specific ICSR in Eudravigilance could originate from. Whilst, the MAHs databases have in fact proved to comply with these requirements satisfactorily.

- Spain also supports the proposal to link PSURs to the knowledge about safety of the product and to create the possibility that PSURs are not required at all. The proposal to not require that PSURs for generic products, herbals and homeopathics are submitted, unless there is a safety issue, is welcomed. Nevertheless, the actual proposal does not take into account the possibility to ask for PSURs of these products after the marketing authorisation after the evaluation of a safety issue. Additionally, Spain suggests making provisions in the new legislation to not require PSURs for products that are already in the market for a long period of time, unless there is a safety issue. Medicinal products for which four 3-year PSURs have been already submitted will accumulate at least 16 years of post-marketing experience and assessed PSURs. It seems reasonable to lift the obligation of further PSURs beyond this point in time unless there is a safety issue. Therefore, the following change in **Article 101f 3** is proposed:

> *3. Unless other requirements have been laid down as a condition for the granting of the marketing authorisation, or as a consequence of the post-marketing evaluation of safety issues, the requirements of paragraphs 1 and 2 shall not apply to products authorised in accordance with Articles 10, 10a, 10c, 13 t o 16 or 16a to 16i of Directive 2001/83/ EC. (...). Also, unless otherwise established, the routine submission of PSURs for all medicinal products may be discontinued after the fourth 3-yearly PSUR.*

b) Provide the legal basis for the existing Member State PSUR assessment work-sharing with a clear coordinating role for the new EMEA pharmacovigilance committee

Article 101f 4 h):

Spain welcomes the proposal for a legal basis for the existing initiative of Member States for PSUR synchronisation and assessment worksharing with a clear role for the new Committee on Pharmacovigilance.

It is also endorsed that an executive summary of the PSUR assessment reports should be made publicly available and what is more relevant, that the rationale for the conclusions and recommendations is made available to the healthcare professionals through Europe. Nevertheless, a clarification on the way the assessment conclusions are made public is needed, as great difficulties in publishing as such all conclusions and recommendations included in PSUR Assessment Reports (ARs) are foreseen when:

- these conclusions are related to the follow up of safety signals which in fact may or may not be confirmed in the following PSURs and corresponding assessments.
- The conclusions are still open to discussions with the MAH or within the Committee on Pharmacovigilance.

Therefore, the opinion of Spain is that only firm conclusions and recommendations in the PSUR ARs leading to specific regulatory measures (i.e. changes in product information) should be published. In addition, it is proposed that only the final conclusions after MAH responses and endorsed by the Committee on Pharmacovigilance should be published.

3.2.8.Strengthen medicines safety transparency and communication

a) Codify legal and guideline provisions on transparency and communication.

Directive 2001/83/EC Article 101i 3

The proposal that as soon as a marketing authorisation holder has the intention to make a public announcement, he shall notify the national competent authorities, the Agency and the EC is endorsed but could preferably be strengthened.

It is essential that in case of important safety information, such as product withdrawals and major restrictions of use of a product, the national competent authorities, the Agency and the EC is informed prior to the any public announcement. Therefore, Spain proposes that the same timelines should be applicable to MAH (this paragraph) and to competent authorities (paragraph 101i 4) as follows:

> *3. As soon as the holder of a marketing authorisation has the intention to make a public announcement relating to important information on pharmacovigilance concerns including product withdrawals and major restrictions to the use of a product he shall give notification to the Member State competent authorities, the Agency and the Commission as soon as they consider public communication and at least 24 hours before their external communication. The marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.*

b) Legal basis would be clarified for the EMEA committee to coordinate (but not replace) the communications of the Member States

The role of the Committee on Pharmacovigilance in co-ordinating public communication in case of safety announcements for no centrally authorised products is supported. But this point should be further clarified. The importance of taking into account the expertise of the Committee should be stressed whilst the role of the Agency should be mostly administrative. Spain therefore proposes the following change in **Article 101 i 5:**

> *5. For substances authorised as medicinal products in more than one Member State, the Agency, via the Committee on Pharmacovigilance, shall be responsible for the coordination between competent authorities of important safety announcements and shall provide timetables for the information being made public. Under the ~~coordination~~ support of the Agency, the Member States shall make all reasonable efforts to agree common safety messages and distribution timetables.*

c) EMEA should maintain an EU portal on the safety of medicines

Directive 2001/83/EC Article 101i 1

Spain can see the added value of a common web-portal for the EU but would prefer that safety was put in perspective of efficacy and risk/benefit. A common EU web-portal, where all documents on efficacy and safety on centrally authorised products, products authorised through the mutual and decentralised procedure and purely nationally authorised products could be found, would therefore be preferable. It should also be clarified that the web based resources present in the European medicines web portal for reporting of adverse reactions should be directed to national competent authorities. Therefore Spain proposes that **Article 101 i 1** should be reworded as follows:

> *1. The Agency shall set up and update a European medicines ~~safety~~ web -portal in collaboration with the Member States and the Commission. By means of the European medicines ~~safety~~ web - portal, the Agency shall make public at least the following information in relation to the safety use of all medicinal products authorised in the Community:*
>
> > *(...)*
> >
> > *(c) Links to information about how to report suspected adverse reactions to medicinal products and forms for their web-based reporting to competent authorities in Member States by patients, healthcare professionals and marketing authorisation holders.*

d) Provision of medicinal product information by companies including to support the development of an EU drug dictionary

Directive 2001/83/EC Article 57 (2)

The aims of the proposed database including product information for all products authorised in the Community would be clarified due to the relevant resources needed to be built and maintained as well as the lack of a clear definition of its value.

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3.2.9 Clearer safety warnings in product information to improve the safe use of medicines:

Introduce a new section in the Summary of Product Characteristics and Patient Information Leaflet on 'key safety information'

Directive 2001/83/EC Article 11 3b / Directive 2001/83/EC Article 59 (ba)

It should be pointed out the need for placing the new safety information in the perspective of the positive effects of the medicinal product, in the SPC as well as in the PL which is of particular importance in the patient perspective.