LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Strategy to Better protect Public Health by Strengthening and Rationalising EU Pharmacovigilance
Public Consultation on Legislative Proposals

Comments by the Medical Products Agency (MPA), Sweden
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Executive Summary of MPA Comments

It is the view of the Medical Products Agency (SE) that there are two important factors that have been essential for the success of the current European regulatory system. The first is the fact the one (or two) individual/team/agency is responsible for a product from the time of application and through out the rest of the life-cycle. The second is the evolution during the last years towards an integration of safety and efficacy assessments pre- and post approval. The Medical Products Agency recognises the need for strengthening the EU pharmacovigilance system. In doing so it is, however, important to ensure that these success factors are not jeopardised.

The overall aim and several of the proposals in the document ”Strategy to Better protect Public Health by Strengthening and Rationalising EU Pharmacovigilance” document are endorsed. The proposed legislative changes to

- ensure the same legal basis for regulatory decisions and possibility to enforce recommendations for all products and in all EU Member states
- rationalise the PSUR procedures
- simplify reporting of ADRs
- provide a stronger legal base for RMPs, PASS, safety referrals and PSUR work-sharing
- harmonise the view in the EU on how to be transparent and how to communicate on safety issues

are welcomed.

However, the proposed changes imply a separation of safety and efficacy making the risk/benefit evaluation and the communication of important information on drugs problematic since the two aspects closely relate to each other. The new legislation should aim at strengthening the safety as an integrated part of both pre-and post authorisation, allowing the benefit-risk assessment for centrally authorised products to continue to be a responsibility of the CHMP and the already appointed Rapporteur’s team. Legislative tools to strengthen implementation of regulatory decisions on pharmacovigilance for MRPs/DCPs/NAPs are supported.

Furthermore, there are some issues of particular importance which are not supported or where clarifications are needed

- The roles and responsibilities of the existing product specific Rapporteur/RMS in the proposed new procedures and approaches need to be maintained
- The proposal to hold public hearings in *every* safety referral (Art 101k) is <u>not</u> supported. To optimize the use of regulatory resources for safety issues impacting on public health, public hearings should only be held in selected cases.
- The proposal to incorporate a new section with key information in the SPC and in the PL (black box warning) is <u>not</u> supported.

- ADR reporting directly from consumers to the MAH, as well as bypassing of the national competent Authorities by direct ADR reporting to the Eudravigilance data base, is not supported.

Moreover, the general organisation of EMEA needs to be considered, in particular the relationship between the responsibilities of the scientific committees and the status of the CHMP in relation to other committees.

Below are presented opinions, comments and questions on the proposed changes within each of the nine main headings.

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

Article 101k (automatic pharmacovigilance referral) *(p 18, 29-31)*:
This new safety referral is welcomed as it clarifies some of the uncertainties in the current safety referral procedure (Article 107). However, there is a need for clarifications:

In Article 101k 1, it should be clearly stated that the conditions to initiate the procedure of this article should be *safety* related.

When is Art 101k to be applied (instead of Art 31/36)?

The EMEA Committee on Pharmacovigilance shall assess the matter and make a recommendation to the CHMP. The CHMP shall then adopt an opinion on the notified safety or risk-benefit concern. If it means that the CHMP will make a *separate* assessment of the issue to form its opinion, this could be questioned.

The purpose and benefit of Public Hearings on every safety referral is not recognised. Since the legislative proposal strengthens transparency and communication in many aspects, public access to information will be guaranteed by several other means.

How will the Lead Rapporteur for the procedure be selected? It may be preferable to involve the Member State which has R/CoR or is RMS for the product, due to previous experience of the specific product.

What is the type of procedure for the MAH's involvement? Will the MAH have an opportunity to present data in response to questions, according to a time table, etc?

How will experiences from the present Art 107 procedure be taken into account?

Is the Commission decision resulting from an Art 101k referral binding, thus precluding the possibility of an Appeal?

Within what time limit shall the Member States announce a decision in accordance with the final decision of the Commission? Should there not be a time limit specified in the article? (Compare article 34.3.)

Reg 726/2004 Article 61 (New EMEA Committee on Pharmacovigilance) *(p 44-45)*:
- Roles and responsibilities:
The rationale to make the legal provisions clear on what safety issues need to be resolved at an EU level is recognized.

In an attempt to analyze the pros and cons of establishing a Committee as compared to maintaining a Pharmacovigilance Working Party (PhVWP) the MPA found that advantages include the potential for consistent scientific opinions on safety issues for all products regardless of approval routes (CAPs, MRPs/DCPs and NAPs); the same legal basis for regulatory decisions and possibility to enforce recommendations for all products and in all EU Member states. Disadvantages include the uncertainty about the mandate of the Committee in relation to the CHMP, i.e. regarding the roles and responsibilities.

It is especially considered that the responsibility for *B/R assessment* in the automatic safety referral regarding Centrally Authorised Products should stay in the CHMP, the Committee having an advisory role.

However, it seems useful to mandate the responsibility for B/R assessment regarding MRPs/DCPs/NAPs to the Committee, or to find other legislative tools to strengthen pharmacovigilance for these products.

For CAPs, it is emphasized that the B/R assessment should continue to be a responsibility of the Rapporteur's team, as safety is an integrated part of both pre-and post authorisation, but benefiting from advice by the experts in the Committee on Pharmacovigilance.

- *Work load:*

As a consequence of the proposed key tasks (safety referral, PASS and PSURs), the work-load for the Committee is likely to increase substantially. *Other established tasks of the PhVWP*, e.g. assessment of signals, assessment of RMPs, guidelines, organisational issues/regulatory/methodological issues, etc, need to be supported as well. Therefore, principles for the overall prioritization and need for type and amount of resources need to be considered.

Key tasks of EMEA Committee on Pharmacovigilance:

1/ Referral recommendations (with hearings) to support CHMP (Article 101 k) *(p 29-31)*
See Above.

2/ Non-interventional Post authorisation safety studies (PASS) (Article 101h) (*p 26-27*):
This proposal is of particular importance for strengthening of Pharmacovigilance. It should be considered to request a PASS (on safety issues) only within the framework of a RMP procedure, i.e. with justification in the Safety Specification and description in the Pharmacovigilance Plan. It seems unfortunate to develop a procedure for PASS separate from the RMP procedure. However, this link between RMP and PASS needs to be further clarified, see below

For centrally authorised products, how would CHMP get feed-back on PASS required at the time of MA? Currently, this is co-ordinated by the Rapporteur. Roles and responsibilities should be clarified.

The PASS reviews (protocols, interim and final reports, abstracts, etc.) will put a considerable workload on the Committee on Pharmacovigilance.

For further comments – see section 3.2.5 below

3/ PSUR coordination (new Article 101f) *(p 24-25)*:
It is emphasized that it will be important to engage the existing R/CoRs or RMSs as Lead Rapporteur, considering their expertise and experience with

the specific products.

For further comments – see section 3.2.7 below

Reg 726/2004 Article 62 (Remuneration of Rapporteurs) *(p 47)*

The remuneration of safety referral and PSUR assessment Rapporteurs will be important for facilitation and motivation of strengthened Pharmacovigilance at the Member State level. Remuneration should be considered for work where a Rapporteur function for safety issues is present, e.g. for RMPs or PASS, and other key tasks, as appropriate.

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

Dir 2001/83 Article 23 (Clear obligation on industry to inform changes to B/R including results of clinical trials and to keep product information up to date including recommendations placed on the EMEA website) *(p 16)*

This proposal is welcomed. However, the proposed added wording "*He (MAH) shall ensure that the product information is kept up to date with the current scientific knowledge including assessment conclusions made public via the European medicines safety web-portal referred to in Article 101i"* should be further clarified concerning what system for supervision by the NCAs should be used in order to see to it that the MAH fulfils these new conditions. This supervision was previously carried out within the PSUR system. It is questioned whether pharmacovigilance inspections will sufficiently cover the supervision of signal detection work being performed and results satisfactory considered for SPC changes.

A revision of the rules and timelines for introducing important updated safety information in the PL should be included in the claims of keeping product information up to date. The existing rules can in practise imply that incorrect information is given in the packages for years.

Dir 2001/83 Article 101 l (List of obligations placed on the Agency, Member States and MAHs) *(p 31-33)*:

General comment: It would be useful to clarify and specify the respective obligations of the stakeholders. However, care should be taken not to regulate in too much detail. There should be room for flexibility on the part of the stakeholder, e.g. with regard to varying characteristics of health care systems in Member States. Also, it should be an expectation that stakeholders could take responsibility for arrangements that will meet overall requirements for good pharmacovigilance practice.

Needs for clarifications include:

- *The Agency*

How will roles and responsibilities for the mentioned tasks be allocated, i.e. responsibilities of the EMEA staff is vs the Committee and NCAs?

For instance, in the Art 101 l (d), the following wording is proposed in order to emphasize the responsibilities of both the Agency and the lead MS competent authority (Rapporteur/RMS)*: "The Lead MS Competent Authority (Rapporteur) and the Agency in collaboration with marketing authorisation holders and the other Member States, monitor the outcome of the risk minimization measures relating to centrally authorised products and those which are the outcome of the procedure of Article 101 k".*

Art 101 l (f): It is equally important to stress the role and responsibility of the Lead National Competent Authority (Rapporteur/RMS) concerning centrally and MRP/DCP authorised products. The role of the Agency needs to be clarified concerning MRP/DCP/NA safety communication.

- *The Member States (MS)*

Clarifications are needed regarding division of responsibilities between EMEA and NCAs, and approaches, schedules and formats for audits.
The MS responsibility for Signal generation in the Eudravigilance (EV) should be better defined as well as the practical procedures for data mining. In addition to the role of the NCAs, the national health care systems and their professionals play a crucial role for the generation and reporting of ADRs. Thus, common European rules must not interfere with nationally tailored systems implemented to safeguard patient safety. The EC proposal does not consider this aspect sufficiently.

101 l (2h and 3): Regular audits of the pharmacoviglance activities are agreed. However, the periodicity (once a year) is too tight from a practical and resource point of view.

- *The MAH*

The establishment of Pharmacovigilance System Master Files (PSMF) will facilitate the monitoring of the Pharmacovigilance systems at MAHs. What will be the policy for MAH's access to EV data?

Dir 2001/83 Article 101b (Good Vigilance Practice (GVP)) *(p 20-21)*

It will be important to develop several aspects of GVP, as mentioned in the proposal. However, developing GVP will likely require a huge and important undertaking for guidelines. Such guidelines need to reflect appropriate scopes, not regulating matters in too much detail. Roles, responsibilities and resources for developing guidance need to be clarified and how they relate to the ICH initiative.

One particular issue regards responsibilities for EV data mining and signal detection/assessment, i.e. the roles of the Agency versus NCAs and their Rapporteur/RMS teams. Art 101 b, 3rd bullet is proposed to read: "*the monitoring by the Agency and the National Competent Authorities of the data in Eudravigilance for signals of new or changing risks in accordance with 101 d"*

Since the guidelines on GVP shall be decided in accordance with article 121 (2), the Medical Products Agency questions whether they are in fact guidelines. It is rather a matter of legally binding legislation (see article 101 b (2)).They should either be decided as guidelines or as legally binding legislation.

3.2.3 Simplify informing the authorities about the company Pharmacovigilance system

Dir 2001/83 Article 1(34), Art 8(3)(ia), Article 101l(4), Article 23, (Pharmacovigilance System Master File (PSMF)) *(p 12, 17, 33)*

The PSMF is likely to be useful and work sparing. Some issues need clarification: Is the PSMF to be assessed/ approved before MA? Who will be responsible to assess the PSMF? Will there be retrospective establishment of PSMFs for all MPs? Will small companies manage to set up PSMFs? How to handle changes of the PSMF, eg. upon switch of the MAH?
This new approach puts greater responsibility on inspection teams, but the PSMF will facilitate their work

Dir 2001/83 Article 111, Reg 726/2004 Article 18 (Inspections) *(p 37, 39, 42-43)*

"A MS shall notify the other MSs, the Agency and the Commission…..where it has conducted a PhV inspection and found serious deficiencies". How to notify this deficiency? Will it be mandatory to send all inspection reports to the Agency? What will be the definition of "serious" deficiencies?

3.2.4 Rationalise risk management planning

Dir 2001/83 Article 1(34) (Definition of the Risk Management system) *(p 12)*

There is an ongoing revision in the EU RMP guideline at the level of the Agency and further a (simplification) project to harmonize RMP procedures with the FDA in the US. Therefore, there may be a need for coordination before a final proposal is possible.

Dr 2001/83 Article 8(3)(iaa) (Clarifies the existing legal requirement to submit a Risk Management (RM) system at the time of MAA for all applications but make it proportionate to risk) *(p 12-13)*

The proposal to establish a legal base to oblige RMP submissions by the MAH is welcomed.
However, to arrive at *proportionate* RMPs, in terms of relevant and sufficient Pharmacovigilance and Risk Minimisation plans, for all new Medicinal Products (and marketed MPs where a safety concern justifies an RMP) will be a challenge. This will likely demand considerable additional guidance and training of staff at both applicant companies and regulatory agencies, and further Scientific Advice (building on experiences from the ongoing Review and Learning project of EU RMPs, launched by the Agency).
Furthermore, the *periodicity* of updates of the RMPs should be considered and formalised in a procedure. See below.

Dir 2001/83 Article 21 (New requirement to annex the Risk Management system to the MA thereby making it legally binding, including any studies included therein *(p 14)*

This is an important proposal in order to make RMPs effectively implemented. It is emphasized that there will be a need to clearly express all commitments in sufficient details in the Annex, regarding the specific pharmacovigilance and risk minimisation measures together with their milestones and timelines.

Dir 2001/83 Article 22 (Replacement of the current "exceptional circumstances MA" by "intensively monitored products") *(p 15)*

It is not understood how the list of "intensively monitored products" could substitute "Exceptional Circumstances" MA. This is an established approval route that can also be based on efficacy issues. Intensive monitoring would rather be an approach used for *all* products and procedures where intensified monitoring is justified in a Risk Management Plan, e.g. advanced therapies, biologicals etc.
A list of all products, in need of intensive monitoring would be useful.
However, the criteria, as stated in Art 22, for a medicinal product to be included in the list of intensively monitored products should be further clarified: e.g. the third criteria "*any conditions or restrictions with regard to the safe and effective use of medicinal product*" is deemed too broad.

Intensive monitoring will be a useful approach for effective safety monitoring of targeted products. However, care must be taken in order not to compromise the proper and careful weighing of benefits versus risks at time of approval. In other words, the requirements for a positive benefit-risk balance should not be relaxed on account of intensified monitoring post-marketing.

Dir 2001/83 Article 127a (New obligation on MS to ensure provisions are in place for the enforcement of RMPs) *(p 41)*

This legislative change could be crucial for the possibility to implement RMPs *consistently* in all EU MSs, of particular importance as regards the Risk Minimisation Plans (building on experiences from RMPs so far). It needs to be considered what the scope of necessary RMP measures should be, i.e. what risk minimisation measures will be deemed required *as a minimum* to ensure *safe and effective use* of medicinal products.

3.2.5 Codify oversight of non-interventional safety studies

Post authorisation safety studies (PASS)
Dir 2001/83 Article 101g (Unambiguous legal basis for requesting PASS for authorised products) *(p 26)*
Dir 2001/83 Article 101h (Detail of how) *(p 26-27)*

Post-authorisation safety studies (PASS) are crucial for effective pharmacovigilance. This proposal has the potential to ensure high quality studies and thereby an improved science base for assessment of drug safety (and effectiveness) and benefit-risk.

A number of uncertainties call for further clarification:

Art 101h(l): What is the regulatory meaning (legal implication) of "recommendations to be taken into account"? Does it mean that a legally binding obligation can be imposed?

The PASS should be linked to the RMP procedure. If the regulatory Agency is requesting a PASS or the MAH is considering a PASS, the MAH should present the PASS within the framework of an EU RMP, with the appropriate justification in the Safety Specification and description of the PASS design, protocol, etc, in the Pharmacovigilance or Risk minimisation Plans of an RMP. The PASS proposed would mostly be expected to be of non-interventional type, and thereby to be assessed by the NCA or by the Committee in the new PASS procedure. However, the PASS may also be interventional, i.e. a randomized safety study or otherwise (according to the Clinical Trial Directive) interventional, in which case the study protocol would have to be assessed by RCT Assessment Boards. The determination of non-interventional is therefore crucial and the clarity of the criteria important. According to experience, the distinction between interventional and non-interventional studies is in real practice sometimes difficult and controversial, leading inappropriately to the classification of some epidemiological (observational) studies as interventional. There is no precise correspondence between the extended and pragmatic definition of non-interventional PASS design in the Volume IX Guideline (which has been expanded to include more complete criteria) and the CT Directive. Therefore, it should be considered to further clarify the definition of a *non-interventional* study design in the CT Directive and to harmonize it with this Directive for PASS and with the relevant guidance documents. Further to that, the procedural requirements, i.e. whether it should be handled by the NCA/Committee on Pharmacovigilance or according to the Clinical Trial Directive, will need to be described in detailed guidance. The setting up of a new, separate, database for PASS versus the present EUDRACT data base could also be questioned.

Thus, the implementation of this new PASS regulation will need a revised definition of the non-interventional study design, thorough guidance and coordination with the approval procedures and RMP procedures.

For further comments – see section 3.2.1 above.

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

Dir 2001/83 Article 101d and 101e (Rationalise expedited single case ADR reporting) *(p 22-23)*
Eudravigilance is of paramount importance for the simplification and rationalisation of ADR reporting. Some issues are of special importance.

- *Eudravigilance (EV)*

It is important, as emphasized above, that the role and responsibility of the Agency versus Rapporteur/Co-Rapp or RMS teams of the respective Member State is clearly defined. In the101d(1), the following wording is proposed in order to emphasize the responsibilities of both the Agency and the

MS competent authority (Rapporteur/RMS)*: "The Agency and the Member State Competent Authorities in collaboration, shall monitor the data…..Community. In the event of a change being detected the identifying party shall inform the Agency and the Lead Member State Authority (Rapporteur/RMS). The Agency shall inform the marketing authorisation holder, the other Member States and the Commission of these findings."*

Further, the MAH's and public's access to product specific information from the EV need to be discussed.

- *ADR reporting rules*

It is stated in the presentation by the Commission (Dr Peter Arlett), December 2007 that for *intensively monitored* drugs reports *from patients* go to the MAH but not *to the National Competent Authority*. This cannot be accepted, especially since the new proposal includes a possibility of the MAH not to report depending on the assessment of causality made by the MAH before reporting an ADR. It is the opinion of the MPA that consumer reporting *should be directed to the NCAs* although this as a consequence may lead to an increased number of reports to the National Competent Authorities.

Article 101e (1): The proposed *definition (of causality) in this section is not supported*. It is recommended that the present definition is kept. This is justified by the fact that every submitted report by a Health Care Professional is submitted due to a *suspected* causal relationship and should therefore be reported by the MAHs. The only acceptable exclusion for reporting by the MAHs could be when the event is occurring before the exposure to the medicinal product

Article 101e (3): This section regarding reporting of medication errors needs further clarification. Medication errors are not always reported within the framework of adverse drug reaction and roles and responsibilities may differ in *different MS.* Responsibilities for medication errors in MSs need to be clarified, especially with the new definition (at any doses).

According to Article 101e (4), a *web-based* reporting by European HCPs directly into EV is proposed. Presently, a quality *assurance of reports is performed by many NCA:s*. This can include causality assessment, requesting additional documentation on the case, analyse of listedness etc. The quality assurance of reports made by NCAs constitutes the basis of the final *quality of the EV database*. From the proposed wording it is unclear if this in the future will be a responsibility of the Agency or the NCA:s with the proposed mutual web-based reporting directly into EV. Please clarify.

What languages will be accepted for HCPs and patient web-based reports directly into EV?

The Agency role for literature monitoring (Article 101e (5)) is supported.

Article 1(ll) (Adverse reaction) *(p 11).*

The proposed definition of an ADR in this article broadens the scope. Please explain the interaction with events not clearly related to the present SPC content. How should such events be brought to the attention of the prescriber? Will there be an analysis of how the influx of new types of ADR cases may influence the present signal detection work? What regulatory measures should be performed and by whom?

Article 1(13) (Unexpected adverse reaction) *(p 11)*

The use of "unexpected adverse reactions" in relation to what is labelled in the SPC has been of value for identifying new signals. Please clarify the reason for deleting this.

Article 1(16) (Abuse of medicinal products) *(p 11)*

Please clarify why this definition should be excluded.

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

Dir 2001/83 Article 101f (Rationalise Periodic safety update reports (PSURs) *(p 24-25)*

The rationalisation of PSURs is supported. However, a number of issues as to its consequences need to be considered.

The interpretation of Article 101f (2) regarding the frequency and dates of submission of the PSURs is unclear. Could the Committee determine the frequency of submission for PSURs for *new* products or will the present rules apply? If individualized (longer) intervals are possible for new products, there is a concern that the pharmacovigilance follow-up of new adverse events may be insufficient. (The relevance of this comment and the expressed concern would depend on the requested clarification.)

It is stated that PSURs should be linked to risk management planning, which needs further clarification. This is because there is no periodic procedure for RMPs as in the situation for periodic safety update reports. RMPs and PSURs are dealing with different issues. RMP documents discuss how to handle known or potential risks, whereas PSUR documents consists of condensed safety data including a review of previously unknown safety signals from ADR reports that may turn into potential or identified risks. There might be situations where no known or potential risks have been identified at the approval and thereby no RMP is required, but PSURs are still needed to monitor the safety profile of the product. It is therefore suggested that RMPs should as much as possible be linked to PSURs. Importantly, repetition of the same information in the two documents should be avoided. A GAP analysis study of the information retrieved in PSURs compared to RMPs should be performed.

Please clarify if all periodic safety update reports, PSURs (Article 101f (1)), within the RMP/DCP procedures, should be submitted to the Agency and not to the responsible NCA (RMS).

As to appointment of a Rapporteur for the PSUR assessment (Article 101f (4e)),valuable knowledge and competence of a specific product is presently built up within the *(Co)Rapporteur's team* pre-approval . This is usually based on a team-work with staff from both pre-and post authorisation performing pre-authorisation assessment of quality,toxicology, pharmacokinetics, efficacy and safety and risk management. In order to avoid a waste of this knowledge, *change of Rapporteur post-approval should be considered only in exceptional cases.* The criteria for such a change should be clarified. A co-ordination with the selected PSUR-RMS already appointed within the on-going PSUR work-sharing project should be considered.

The role of the Committee on Pharmacovigilance to steer work sharing and to adopt Assessment Reports will be a huge (key) task. There will be a need to prioritize the tasks of the Committee.

PSURs for generics are proposed as not mandatory, unless specific condition of the marketing authorisation. If the MAH for the innovator product withdraws the marketing authorization (for a non-safety reason), how would this be handled?

PSURs for old well-established products are proposed as not mandatory, unless specific condition of the marketing authorisation. When new products are approved, new situations could arise for old products already on the market (e.g. interactions). If there are no PSURs for old products, how would these events be found?

3.2.8 Strengthen medicines safety transparency and communication

Dir 2001/83 Article 101i (Strengthening transparency and communication) *(p 27-28)*

Generally, a harmonised view on transparency and communication in the EU is supported. The establishment of information web portals will have a great potential and is very welcomed. Some issues need clarification.

It will be important that the new legislation on transparency measures takes into account the *existing varying legislative environment in the different MSs*.

In some situations, despite legislative changes and new guidelines, it will be necessary for a NCA to communicate on safety issues, e.g. respond to enquiries from the public/media in an un-coordinated manner to avoid mistrust in the EU system. This is to take account of the varying characteristics of both regulatory and health care systems in the Member States.

As to the Agency web-portal, the list of topics for information to be made public by the Agency (as specified in Article 101i) could be expanded with new key safety information, USR SPC changes, etc.

Further, it would be preferable that safety information were put in *perspective of efficacy and risk/benefit.* A common EU portal, where *all* documents on efficacy and safety on CAPs, MRPs, DPs and NAPs could be found, would therefore be advantageous.

It should be clarified if the safety-portal would be an *extension of the Eudrapharm database* which could be an advantage. The content and the *goal of the EU safety web-portal* needs to be further clarified and detailed and the *language difficulties* should be considered and clarified. One missing aspect is if, and in such a case how, safety signals under evaluation are to be communicated to alert the HCPs and patients on the ongoing concern to encourage ADR reporting and to make possible intermediate recommendations when needed.

Art 101i:

(1a) In addition to the members of the committees, *external experts* who participate in the meetings should be mentioned.

(1b) In addition to publication of conclusions and recommendations of the PhV Assessment Reports, we propose that the rational for the decisions is published. This executive summary would be suitable for translation in all official languages and subsequent publication on national competent authorities' websites. **(1c)** It is essential to clarify that health care providers and the public from different MSs, via the portal can *reach the NCA:s websites* and get information on how to report ADRs and get other important information in their respective languages. All this information should be available through national medicines safety web-portal. (See 2).

(1d) This statement should be clarified. Does it mean the full risk management plan or a summary of this document? Furthermore, there should be a harmonisation of how the RMPs are presented in the EPAR and PARs to facilitate the reading and the understanding among non-regulators.

(1e) If an intensive monitoring list is set up it should be published on the safety web portal

(1f) The relevance of such a list (of QPs) needs to be explained particularly taking into account the work load to keep such a list updated

(1g) In addition, in accordance with the PhV assessment reports, an executive summary of the PSUR assessments should be made publicly available. It

is important that the rational for the conclusions and recommendations is included.

(2a) Se above point (1d)
Add **(2c)**: Information about how to report suspected adverse reactions to medicinal products and forms for their web-based reporting by patients, healthcare professionals and marketing authorisation holders"

(5) The role of the Agency contra the Committee on Pharmacovigilance in coordinating the communication in case of safety announcements should be clarified. It is important that the expertise in the committee is taken into account.

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

Reg 726/2004 Article 57(2) *(p 43-44)***, Dir 2001/83 Article 11** *(p13),* **Dir 2001/83 Article 54** *(p18-19),* **Dir 2001/83 Article 59** *(p19)* **(Clear legal provisions on the provision of medicinal product information to support the development of Eudrapharm and EU PhV medicines terminology, Strengthen Product Information)**

The reformation of Product Information to prescribers and patients is of utmost importance. However, the present proposal is critically commented.

The proposal to incorporate a new section with key information in the SPC, and in the PL (black box warning), is not supported. This view is primarily based on the perceived difficulty to select and present specific relevant pieces of information as key data for different types of products, and further that it could be disadvantageous (for patient compliance) to highlight only adverse effects in such a visible way. The added value of key safety information in the SPC and PL is also questioned since the most common safety concern might not be the most relevant one for the individual patient. However, improved dissemination of information on the safe and effective use of a product is of great importance. It is proposed that, other means of conveying such safety information are considered and promoted, e.g. IT based prescribing information systems and, for patients, the use of alert cards. As to the PLs, it is of particular importance to enhance the safety information in the perspective of the positive effects of the drug. A balanced benefit/risk information would be of added value to the patient.

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. See 101 e, 3, second paragraph "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.

As a general comment, the SPCs have over time become more extensive and complex, and the PLs have come to focus increasingly on adverse drug reactions. A future revision of the SPC/PL guidelines is recommended where focus should be on achieving innovative and user friendly information on how to use medicinal products more safely and effectively. This revision should be undertaken in close co-operation with health care professionals and patients.

General provisions

Article 101 q

The reference to article 121 (2a) is incorrect since there is no paragraph 2a in article 121.