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

Comments by the CHMP
January 2008

Overall comments
The CHMP reviewed the EC proposal ”Strategy to Better protect Public Health by Strengthening and Rationalising EU Pharmacovigilance” through two discussion sessions during its January meeting. The overall/pivotal comments are summarized below. In addition, more detailed comments from the review are presented for the nine different themes in chapters 3.2.1. - 3.2.9. **Pivotal comments:** The CHMP endorses the overall aim of the EC proposal. The need to strengthen the legal framework regarding nationally approved products is recognised. The CHMP is, however, deeply concerned that the proposed legislative changes will have a negative public health impact in relation to Centrally Authorised Products (CAPs). The CHMP considers that the centralised procedure for approval and safety surveillance of drugs has been very successful. There are at least two fundamental reasons for this. *Firstly,* the system with dedicated Rapporteur teams that are responsible for a product from the time of application and throughout the rest of the life-cycle is vital. This can be exemplified by the experience from the CAPs that have now undergone more than 100 type II variations. The importance of accumulated knowledge of a product for continuous benefit-risk assessments should not be underestimated. Also, it is of relevance that one of the current criteria for appointing a specific Rapporteur is that his/her team should be able to handle Pharmacovigilance issues, e.g. related to RMPs (and other maintenance work). Based on this, a Pharmacovigilance assessor is part of the prelicensing team. *Secondly*, there has been a continued evolution during recent years towards an integration of safety and efficacy assessments pre- and post approval. The introductions of the EU Risk Management Plans as well as the “Conditional approval” are important parts of this. Regulators continued involvement in post-approval drug development with respect to both the efficacy and safety profile of a medicinal product is now well established. Any new pharmacovigilance system for CAPs should ensure that these two essential features are maintained. The advent of a new EMEA Committee on Pharmacovigilance with responsibility for some (benefit)-risk assessments for CAPs is not supported. The risk for divergent views and/or duplication of work is obvious. This cannot be in the interest of Public Health. Attempts to separate decisions pre- and post approval or into efficacy or safety issues are steps in the opposite direction from the successful development we have seen during the last 10 years.

Hence, regardless of whether a new Committee is created or not the CHMP strongly suggests that for CAPs the current system is maintained, i.e. the CHMP retains responsibility for the benefit/risk assessment pre- and post-approval with the Pharmacovigilance Committee/WP providing important advice on safety related issues.

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

The CHMP endorses the overall aim of the EC proposal ”Strategy to Better protect Public Health by Strengthening and Rationalising EU Pharmacovigilance”. Further strengthening the legal support to ensure that agreements on safety issues regarding nationally approved products are implemented in all Member States are supported. However, this is not an issue for CAPs. As been pointed out above, the CHMP finds that the proposed mandate of the EMEA Pharmacovigilance Committee needs to be critically reviewed in relation to the roles and responsibilities of the CHMP. The CHMP considers that the CHMP should maintain its responsibility to assess and give a scientific opinion of the benefit-risk balance for CAPs, also regarding postmarketing safety issues.

The present proposal for the EMEA Pharmacovigilance Committee to perform the assessment of safety issues in a 90-day procedure and to recommend regulatory action (e.g. suspension or revocation of MA) in fact constitutes a benefit-risk assessment. Even though this would be a recommendation for the CHMP, the conduct of the full procedure in the Committee will preclude a thorough benefit-risk assessment in the CHMP, e.g. due to constraints in time and practical arrangements, etc. Therefore, the CHMP expresses its serious concerns that the proposed procedure for CAPs will create an unfortunate separation of responsibilities and a competitive situation between the CHMP and EMEA Pharmacovigilance Committee. The CHMP considers that the present system should be retained, i.e. that the CHMP should keep the role and responsibility for benefit-risk assessments throughout the complete product life cycle, including when specific safety issues arise for CAPs. However, the EMEA Pharmacovigilance Committee should have the role to deliver the best possible, scientific advice to the CHMP for the safety issues in question.

The CHMP considers that the present legislative proposal does offer a useful solution in order to strengthen Pharmacovigilance and regulatory decisions for the non-CAPs, i.e. MRPs/DCPs/NAPs. For these products the EMEA Pharmacovigilance Committee will be essential to deliver assessment in the safety referrals.

In summary, the mandate of the EMEA Pharmacovigilance Committee for benefit-risk assessments of CAPs as proposed is <u>not</u> supported; the role and responsibility of the Rapporteur teams and CHMP for CAPs’ throughout the product life cycle should be retained; while the EMEA Pharmacovigilance Committee should have the role to deliver best possible scientific advice for the safety assessment. For MRPs, DCPs and

NAPs, however, the EMEA Pharmacovigilance Committee together with the new safety referral procedure will be useful and important.

Thus, it is concluded by the CHMP that the EMEA Pharmacovigilance Committee should have different mandates for CAP and non-CAP products, respectively.

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

- The Roles and responsibilities of the Rapporteurs in relation to the Agency (EMEA) should be clarified in the proposal, e.g. regarding signal detection and assessment in the Eudravigilance, and follow up of commitments in Risk Management Plans.

- The implication of the proposed new and established key tasks for the workload of the EMEA Pharmacovigilance Committee is of concern. From the perspective of the CHMP, what will be the capacity to deliver important requested safety advice regarding e.g. PASS, RMPs etc?

- As to Article 101c, in continuation at the end of the Article it is proposed to add: "which should be used to develop under the control of the National Competent Authorities an active-interactive pharmacovigilance system. This comment is meant to encourage legislation for use of private money to support strengthened Pharmacovigilance.

3.3.3 Simplify informing the authorities about the company Pharmacovigilance system

- The CHMP endorses the proposal, no specific comments.

3.2.4 Rationalise risk management planning

- Overall, the CHMP endorses the strengthened legal base for Risk Management Planning. The CHMP recognizes the need for further guidance and training of both applicants and regulators in order to achieve descriptions of Risk Management Systems (EU RMP) that are *proportionate* to the profile of the specific product.
- The CHMP does not see the rationale for *replacing* Exceptional Circumstances MA by intensively monitored products. Approval under Exceptional Circumstances could be justified by issues not only relating to safety but also efficacy. The CHMP finds that there should be no change in the proposed legislation of the Exceptional Circumstance MA mechanism.

- The concept of intensive monitoring of targeted products is endorsed, being a valuable approach for strengthened pharmacovigilance for certain products as justified in the RMP. However, the criteria for including a product in the list of intensively monitored products, as specified

in Art 22, seem a bit broad and should therefore be defined more closely.

3.2.5 Codify oversight of non-interventional safety studies

- The CHMP welcomes the strengthened legal base for and management of post-authorisation safety studies. The experiences so far, collected through the CHMP Review and Learning Project for EU RMPs, imply that Post-authorisation Safety Studies (PASS) need to be more strictly regulated and assessed within approval procedures and monitored for progress and fulfilment of commitments post-launch.

- The CHMP considers that the PASS, justified by an important safety issue, should be linked to the RMP procedure. Thus, the safety issue in question should be motivated in the Safety Specification and adequately described in the Pharmacivigilance and/or Risk Minimisation Plans of the RMP. The present proposal strengthens and clarifies theses requirements.

- Further, the PASS proposed would mostly be expected to be of *non-interventional* type, and thereby to be assessed by the NCA (if conducted in one single Member State) or by the EMEA Committee on Pharmacovigilance (if performed in more that one Member State) in the proposed PASS procedure. However, the PASS may also be *interventional*, i.e. a randomized safety study or otherwise (according to the Clinical Trial Directive) deemed as interventional. In this latter case the study protocol would have to be assessed by RCT Assessment Boards in the respective Member State.
The determination of non-interventional status of the PASS is therefore crucial and the clarity of the criteria for definition of non-interventional vs interventional designs important. According to experience, the distinction between non-interventional and interventional studies is in real practice sometimes difficult and controversial, with the disadvantage of classification for 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 (to include more complete criteria corresponding to the practise for epidemiological studies) and the CT Directive. Therefore, the CHMP proposes that the definition of a n *interventional* vs a *non-interventional* study design in the CT Directive should be revisited and revised and that a revised definition should be harmonized with this new Directive for PASS (and with the Volume IX).

- Further to that, the procedural approaches, i.e. whether the PASS should be handled by the NCA/EMEA Committee on Pharmacovigilance or according to the Clinical Trial Directive, will need to be described in detailed guidance. The rationale for setting up of a new, separate, database for non-interventional PASS versus the present EUDRACT data base for interventional studies could be questioned.

- In summary, the CHMP considers that the implementation of this new PASS regulation will need a revised definition of the non-interventional study design in the existing RCT Directive and in the proposed PASS Directive, thorough guidance and coordination with the Approval and RMP procedures.

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

- The CHMP recognizes the great potential value of the Eudravigilance to optimize Pharmacovigilance on the basis of spontaneous ADR reporting in the EU.

- The CHMP considers that the roles and responsibilities for the Rapporteur/RMS teams for signal definition, assessment and follow-up in the Eudravigilance need to be clearly reflected in the new legislation.

- The CHMP does not endorse that the consumer reporting of ADRs is directed to the MAH. It is proposed that all reports should be channelled through the NCAs, in order to simplify and facilitate this reporting.

- The CHMP does not find the proposed long-term direct and web-based ADR reporting from Health Care Professionals to the Eudravigilance as useful. The CHMP considers that ADR reporting to national and regional centres, where available, within Member states, should be maintained, in order to enhance reporting compliance and to facilitate the completeness and increase the quality of the reports to be entered in the Eudravigilance.

- The CHMP does not endorse the proposed changes to the definitions of adverse drug reactions (ADR) in Directive 2001/83/EC Article 1(11), 1(13), 1(16). Changes to these definitions will bring the EU definition out of line with international (ICH, WHO) definitions in this field and will be a major hindrance to signal detection and PhV using world wide information. Moreover, change of these definitions will make historical comparison af ADRs difficult. If these proposals are made in order to accommodate medications errors as an ADR it is suggested to add a new point clarifying that medication errors is and ADR and should be reported as such

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

- The CHMP endorses the proposal on rationalisation of PSURs, especially making its practise more flexible.

- The CHMP sees no need for the EMEA Committee on Pharmacovigilance to appoint a new Rapporteur for assessment of the PSUR. The Committee should mandate the original Rapporteur/RMS to take on this role. Besides this being most efficient, the CHMP finds that the existing knowledge and experience of the product on the part of the Rapporteur/RMS are very important in the integrated assessment of risks and benefits.

3.2.8 Strengthen medicines safety transparency and communication
- The CHMP fully supports the aim to increase transparency and considers many of the proposals valuable. The future success of the EU system will largely depend on our ability to explain benefit-risk assessments to stakeholders such as patients, health care providers, industry, reimbursement bodies etc. Public hearings may very well be one way to increase transparency for all committees at the EMEA. However, the CHMP questions the proposal of Public Hearings in *all* safety procedures. This does not seem to be the best use of available resources. The CHMP welcomes a legislation that would open up for the possibility to have public hearings but the legislation should not micromanage when and how this should be handled. Instead, a "best practise" should evolve with time also taking the experience from other regulatory agencies around the world into consideration.
3.2.9 Clearer safety warnings in product information to improve the safe use of medicines
- The structure of the SPC and PL today is such that it aims to balance safety and efficacy information. Furthermore, in section 4 of the SPC important guidance to the prescriber is provided while section 5 largely contains a summary of the characteristics. The CHMP does not support the proposal to repeat/highlight key safety information (including a black box in the PL). Firstly, making the SmPC even more extensive may be counter productive. Secondly, the difficulty to select relevant key safety information is foreseen. What is more important for some patients may be less to others. There is also an obvious risk that safety information not included in this new section is not sufficiently considered Thirdly, it is likely beneficial for patient intake compliance to present safety information in the context of benefits/efficacy, especially in the PL, rather than in isolation. Thus, the CHMP expresses concerns about the appropriateness of the scope and methods in the present proposal. The CHMP identifies a need to re-assess the entire structure of the EU Product Information but understands that this is beyond the scope of the current proposal.