The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

London, 5 April 2004
Doc. Ref: EMEA/CPMP/4285/04/Final

Handling by the CPMP of Safety Concerns for Pre- and Post-Authorisation Applications Submitted in Accordance with the Centralised Procedure

I Introduction

In the context of the further development and implementation of the EMEA Risk Management Strategy, the EMEA undertook a review in 2002 of the lessons learnt in relation to the handling by its Scientific Committee, the CPMP, of safety concerns for Centrally Authorised Products (CAPs).

Based on this casework history areas for further improvement were identified which lead to the adoption by the CPMP in March 2003 of a revised procedure for the handling of safety concerns for pre- and post-authorisation applications, processed in accordance with the centralised licensing route. Subsequently, a consultation phase with the Heads of Agencies of the National Competent Authorities (NCAs) was undertaken. All necessary practical arrangements to be put in place were finalised in the beginning of 2004.

II Objective to Be Achieved

The overall objective to be achieved is the development of a better equipped system capable of handling safety concerns both pre- and post-authorisation in a more efficient and timely manner. This should result in reinforced scientifically robust decision-making.

It should allow the CPMP to have at its disposal, during its discussions, all necessary tools in order to enable the Committee to adequately manage its responsibilities and to allow the individual Members to perform their duties as described in Community legislation. Consequently, the revised procedure should be capable of providing reinforced support to (Co)-Rapporteurs and CPMP Members in their decision-making on clinical safety issues, both pre- and post-authorisation.

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III Prerequisites to Be Fulfilled

In order to meet this overall objective the following prerequisites need to be fulfilled:

- The best expertise at European Union (EU) level should be made available to the CPMP.
- Taking into account the limited resources available at EU level, a better use of the available expertise should be achieved.

IV Handling of Safety Concerns by the CPMP

IV.1 General Framework

The revised procedure will:

- Strengthen the collaboration between pharmacovigilance and pre-authorisation functions supporting the (Co)-Rapporteur to provide for a more structured involvement of pharmacovigilance staff in the pre-authorisation evaluation phase.
- Improve the availability of sufficient and adequate specialised expertise at EU level to strengthen the conduct of pharmacovigilance both pre- and post-authorisation and to cope with an increasing workload.
- Facilitate the role of the Pharmacovigilance Working Party (PhVWP) as a support to the CPMP in its decision-making.

In order not to create a double-standard system, the same specialised expertise is made available to the PhVWP for the PhVWP's discussions on safety issues for non-Centrally Authorised Products (non-CAPs).

IV.2 Characteristics

IV.2.1 Pre-Authorisation Phase

- The collaboration at NCA level between pharmacovigilance staff and pre-authorisation staff of the Rapporteur's and Co-Rapporteur's assessment team needs to be strengthened, leading to the submission, in accordance with the current timeframes, of integrated assessment reports to the CPMP. In those situations where such close interaction at NCA level would not be possible, the (Co)-Rapporteur could consider involving specialised expertise available at EU level (see also below).
- The involvement of additional scientific expertise in terms of specialised experts is triggered by the Rapporteur, the Co-Rapporteur or any other CPMP Member[1], after agreement by the CPMP[2]. However, for certain products such involvement is recommended, e.g. orphan drugs, emerging therapies, new compounds of a completely new therapeutic class, compounds for which risk management plans are submitted by the applicants. The subsequent involvement of the PhVWP is decided by the CPMP.

[1] This does not exclude the possibility for pharmacovigilance experts involved in the pre-authorisation assessment to identify the need for specialised expertise involvement. However, any request needs to be channelled through the CPMP Membership.

[2] Any involvement of specialised experts can only be initiated once the EMEA has been informed and has signed-of such involvement.

- These experts are chosen by the CPMP on recommendation of the (Co)-Rapporteur amongst the pool of experts available to the Committee. Selection criteria will take into account the type of questions asked by the CPMP, the profile of the experts as well as their workload. As stated above this pool of experts is also available for the (Co)-Rapporteurs who cannot benefit from a joint assessment by pre-authorisation and pharmacovigilance experts at their national level.
- The specialised experts need to work closely with the (Co)-Rapporteurs and the PhVWP (if involvement of the PhVWP has been decided by the Committee) and need to make available to the CPMP within a set timeframe a written report, providing responses to the questions raised by the CPMP, in order for the CPMP to take into account during their decision-making. The specialised experts will attend the CPMP discussions.
- In situations where an involvement of the PhVWP has been decided by the CPMP, a peer review is undertaken by the PhVWP within a set timeframe, prior to the submission of the specialised experts' reports to the CPMP,. The specialised experts will attend the PhVWP discussions. If such peer review leads to the need to revise the initial report, the specialised experts will implement the agreed changes in accordance with a set timeframe. In those (rare) situations where divergent viewpoints were expressed at PhVWP level such divergence will be recorded in the revised report prepared by the specialised experts.

Attachment 1 provides further details on the involvement of additional scientific expertise in the pre-authorisation phase.

IV.2.2 Post-Authorisation Phase

- The need to involve additional scientific expertise in the handling of safety concerns during the post-authorisation phase can be identified by the Rapporteur, the Co-Rapporteur or any other CPMP Member[3]. The Rapporteur is mandated by the CPMP to decide on the level of additional scientific expertise to be involved, which is either (1) the need to refer the issue to the PhVWP, or (2) the need to involve, in addition to the PhVWP, specialised experts[4].
- Situations which warrant involvement of the PhVWP depend on the impact on the benefit/risk balance of the medicinal product.
- Situations which warrant the involvement of specialised experts in addition to the input from the PhVWP would only arise in certain situations.

[3] This does not exclude the possibility for pharmacovigilance experts involved in the post-authorisation assessment to identify the need for additional scientific expertise involvement. However, any request needs to be channelled through the CPMP Membership.

[4] Any involvement of specialised experts can only be initiated once the EMEA has been informed and has signed-of such involvement.

- Tthe specialised experts are chosen amongst the pool of experts available to the CPMP. It should, however, be noted that a mandate is given by the CPMP to the Rapporteurs as to the identification of the specialised experts to be involved in addition to the PhVWP. Selection criteria will take into account the type of questions asked, the profile of the experts, as well as their workload.
- Three situations can occur in the post-authorisation phase:
  - When no involvement of additional scientific expertise is needed, the Rapporteur submits a written report to the CPMP within a set timeframe, including recommendations for regulatory action.
  - When PhVWP involvement is needed, the Rapporteur's PhVWP representative will take the issue forward and is responsible for the preparation and follow-up of the discussion at PhVWP level. The Rapporteur in collaboration with his/her PhVWP representative will put precise questions to the PhVWP for discussion at PhVWP level.

    The PhVWP can also identify the need for specialised experts' involvement. The Rapporteur has to decide on involvement of such specialised experts[5].

    The Rapporteur's PhVWP representative subsequently prepares a written report on the basis of the outcome of the discussions at PhVWP level, including the PhVWP recommendations for regulatory action, and presents such report to the CPMP. In those (rare) situations where divergent viewpoints were expressed at PhVWP level such divergence will be recorded in the report.
  - When involvement of specialised experts is needed in addition to the involvement of the PhVWP, the specialised experts should provide to the Rapporteur's PhVWP representative written responses to the questions raised. The Rapporteur's PhVWP representative will ensure that a written report is available to the PhVWP. The specialised experts will attend the PhVWP discussions.

    The PhVWP will peer review such report and in addition propose to the CPMP recommendations for regulatory action.

    The Rapporteur's PhVWP representative subsequently prepares, where relevant, a revised report, including the PhVWP recommendations for regulatory action, and presents such report to the CPMP. In those (rare) situations where divergent viewpoints were expressed at PhVWP level such divergence will be recorded in the report. Specialised experts will also attend the CPMP discussions in addition to the Rapporteur's PhVWP representative.

Attachment 2 provides further details on the involvement of additional scientific expertise in the post-authorisation phase.

[5] Any involvement of specialised experts can only be initiated once the EMEA has been informed and has signed-of such involvement.

IV.3 Roles and Responsibilities of the Different Parties

IV.3.1 Pre-Authorisation Phase

Role and responsibilities of the CPMP

The CPMP has the responsibility for providing the opinions of the Agency in relation to the quality, safety and efficacy of human medicines.

The Committee can benefit from additional scientific expertise made available through the specialised experts and the PhVWP to achieve reinforced scientifically robust decision-making.

The CPMP shall decide in each situation:

- If specialised scientific input is necessary;
- If yes,
  - which expert(s) should be involved;
  - what questions need to be addressed;
  - within what timeframe a reply is needed.
- If involvement of the PhVWP is needed (to be considered on a case-by-case basis).

Examples of such questions are:

- To specify any safety areas to be monitored in addition to those already identified by the (Co)-Rapporteurs or CPMP Members.
- To make specific recommendations to the CPMP as to whether spontaneous reporting systems alone will be sufficient in the post-authorisation phase and, if not, what additional specific tools need to be envisaged.
- To comment on the frequency and nature of spontaneous and periodic reporting if the standard measures need to be intensified, e.g. to report on pregnancies in case a risk management plan for a teratogenic product includes measures to prevent such pregnancies, to shorten the PSUR cycle for high risk products (e.g. 3 months), etc.
- To comment on any other form of intensive pharmacovigilance monitoring.
- To comment on the appropriateness, feasibility and design of post-authorisation safety studies to be done by Marketing Authorisation Holders (MAHs).
- To comment on risk management plans submitted by pharmaceutical industry or propose a request for such risk management plans, if justified.

Role and responsibilities of the (Co)-Rapporteurs

The (Co)-Rapporteurs are appointed by the CPMP. They take the lead in the scientific assessment of the dossier submitted by the applicant. Their deliverable is the provision of assessment reports, in accordance with set timeframes, for discussion by the CPMP, leading to the development of the CPMP Assessment Report, and where applicable, the European Public Assessment Report (EPAR).

Role and responsibilities of the specialised experts

The role and responsibilities of the specialised experts is to support the CPMP, (Co)-Rapporteurs and PhVWP on (1) pre-clinical issues with a potential impact on the post-authorisation phase and (2) clinical safety issues.

More specifically such experts should, within set timeframes, provide responses to any questions identified by the CPMP. The deliverable is the submission of a written report to the CPMP, or the PhVWP if involvement of the PhVWP was decided by the Committee. In case of such involvement the specialised experts will subsequently present the outcome of the discussion at PhVWP level as a written (revised where relevant, including where applicable, any divergent views expressed at PhVWP level) report to the CPMP in order for the Committee to take this into account during its decision-making. The responses to the CPMP should be clearly presented as recommendations to the Committee. It should be recognised that these will be recommendations and that the CPMP would not necessarily be obliged to accept them. The specialised experts will subsequently attend the discussions at CPMP level.

As a general principle it is important to emphasise that whereas the specialised experts are responsible for a given topic (i.e. providing, with involvement of the PhVWP (where relevant), responses to the question(s) raised by the CPMP), the (Co)-Rapporteurs remain in charge of the file. In addition, specialised experts do not take any part in the decision-making at CPMP level.

Role and responsibilities of the PhVWP

When requested by the CPMP, the role and responsibilities of the PhVWP are to provide support to the Committee by peer reviewing, in accordance with set timeframes, the reports prepared by the specialised experts.

IV.3.2 Post-Authorisation Phase

Role and responsibilities of the CPMP

The role and responsibilities of the CPMP in the post-authorisation phase do not differ from those in the pre-authorisation phase. Consequently the CPMP is the legal forum for providing the opinions of the Agency on post-authorisation activities.

In order to achieve reinforced scientifically robust decision-making the Committee can benefit from additional scientific expertise made available through the PhVWP and specialised experts.

Taking into account the rather short timeframes which apply to the majority of post-authorisation activities, and acknowledging that urgent situations could arise which warrant immediate action to be taken, the revised arrangements should take into account such tight timeframes.

Therefore, a mandate is given by the CPMP to the Rapporteurs to decide on the involvement of additional scientific expertise to assist the Committee in the scientific evaluation process.

Role and responsibilities of the (Co)-Rapporteurs

The pre-authorisation Rapporteur takes the lead in the post-authorisation phase, evaluating all issues related to CAPs. The involvement of the pre-authorisation Co-Rapporteur is decided by the CPMP on a case-by-case basis.

The need to involve additional scientific expertise in the handling of safety concerns during the post-authorisation phase can be identified by the Rapporteur, the Co-Rapporteur or any other CPMP Member.

Rapporteurs will be mandated by the CPMP in relation to the handling of safety concerns in the post-authorisation phase to decide on the need (1) to refer the issue to the PhVWP and (2) to involve, in addition to the PhVWP, specialised experts.

- Need to refer the issue to the PhVWP:

  Situations for which involvement of the PhVWP may be required, depending on the impact on the benefit/risk balance of the medicinal product are:

  - Follow-up of safety related issues already considered by the PhVWP in the pre-authorisation phase.
  - Follow-up of risk management plans agreed upon by the CPMP during the adoption of the Opinion on the initial application for marketing authorisation.
  - Follow-up of post-authorisation safety studies.
  - Safety signals of potential public health impact which need to be confirmed or quantified.
  - Confirmed or quantified safety signals.
  - Safety issues which could lead to a substantial change in the use of the medicinal product or medical practice.

  In the above situations leading to a decision by the Rapporteur to involve the PhVWP, the Rapporteur is responsible for:

  - Requesting his/her PhVWP representative to take the issue forward.
  - Drafting, in collaboration with the PhVWP representative, the questions that need to be addressed by the PhVWP.
  - Specifying the timeframe for addressing such questions.

- Need to involve specialised experts:

  In certain situations the Rapporteur can decide to involve specialised experts, in addition to the PhVWP.

  Such situations could be:

  - Follow-up of issues which required the involvement of specialised experts in the pre-authorisation phase.
  - New issues arising in the post-authorisation phase which warrant the involvement of specialised experts.

  In the above situations the Rapporteur is responsible for:

  - Requesting his/her PhVWP representative to take the issue forward.
  - Identifying which specialised expert(s) should be involved in addition to the PhVWP.

- Drafting, in collaboration with the PhVWP representative, the questions that need to be addressed by such expert(s).
- Specifying the timeframe for a reply.

Role and responsibilities of the PhVWP

When the involvement of the PhVWP is needed, the role and responsibilities of the PhVWP are to address the questions put to the PhVWP within set timeframes and to propose to the CPMP recommendations for regulatory action.

The PhVWP can also identify the need for involvement of specialised experts.

As stated above, the Rapporteur's PhVWP representative is responsible for preparing a written report (including, where applicable, any divergent views expressed at PhVWP level) on the basis of the outcome of the discussions at PhVWP level, and presenting such report to the CPMP.

In those situations which require the involvement of specialised experts, the Rapporteur's PhVWP representative is responsible for ensuring that a written report is available within a set timeframe, which includes the replies provided by the specialised expert(s) to the questions raised. After discussion at PhVWP level, the Rapporteur's PhVWP representative, in collaboration with the specialised expert(s), is responsible for providing the outcome of the discussions as a written (revised where relevant, including, where applicable, any divergent views expressed at PhVWP level) report to the CPMP, including the PhVWP recommendations for regulatory action.

It should be noted that the CPMP would not necessarily be obliged to accept the responses and the recommendations for regulatory action, but will have to take them into account during its decision-making.

The Rapporteur's PhVWP representative will attend the discussions at CPMP level but will not take any part in the decision-making at CPMP level.

Role and responsibilities of the specialised experts

In the situations requiring involvement of specialised experts, the questions put to the specialised expert(s) will have to be answered within a set timeframe. The specialised expert is responsible for ensuring that his/her replies are made available to the Rapporteur's PhVWP representative in order to allow for the availability of a written report for discussion at PhVWP level. Any revision of the report will have to be done as stated above. The specialised expert(s) will subsequently attend the discussion at CPMP level and will not take any part in the decision-making at CPMP level.

IV.4 Follow-up

The procedure will be carefully monitored in order to introduce, where necessary, any corrective measures. Furthermore, the outcome of the EU Review 2001 of pharmaceutical legislation as well as the developments at international level (e.g. in relation to the ICH initiative on Pharmacovigilance Planning) will be closely looked at and, where relevant, changes will be introduced in the procedure.

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London, 5 April 2005
Doc. Ref: EMEA/CPMP/4359/04/Final

Attachment 1

Pre-Authorisation Phase: Applications for Marketing Authorisation

Step of the procedure	Responsible	Task
Day 1-70	(Co)-Rapporteur	▪ To ensure close collaboration between pre-authorisation and pharmacovigilance functions within his/her assessment team, leading to the availability both at Rapporteur and (Co)-Rapporteur level of an integrated assessment report. ▪ To involve, whenever needed, specialised experts in the assessment.
Day 70	(Co)-Rapporteur	▪ To consider involvement of specialised expert(s).[1,2] ▪ To identify such expert(s). ▪ To identify the question(s) to be addressed by the expert(s) within a specific timeframe.
Day 90	CPMP	▪ To agree on the proposals made by the (Co)-Rapporteur[3, 4]. ▪ To decide on the involvement of the PhVWP (case-by-case basis).
Day 115	Specialised expert(s)	▪ To submit the report(s) to the PhVWP[5]/CPMP, with a copy to the (Co)/Rapporteur and the EMEA.

1 For instance in case of disagreement between the Rapporteur and the (Co)-Rapporteur on safety issues.
2 For certain products involvement of the specialised experts and the PhVWP is recommended, e.g. orphan drugs, emerging therapies, new compounds of a completely new therapeutic class, compounds for which risk management plans are submitted by the applicants.
3 When no involvement of specialised expert(s) was identified by the (Co)-Rapporteur, CPMP Members still have the opportunity to do so (or the pharmacovigilance expert(s) involved in the pre-authorisation assessment who should put the request to the CPMP Member). Subsequently, the CPMP has to agree with the CPMP Member(s) proposals.
4 Any involvement of specialised experts can only be initiated once the EMEA has been informed and has signed-of such involvement.
5 When involvement of the PhVWP has been decided by the CPMP.

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Step of the procedure	Responsible	Task
Day 120[5]	PhVWP[5]	▪ To peer review the report(s) prepared by the specialised expert(s). [5]
Day 120[5]	Specialised expert(s) [5]	▪ To submit the (revised) report(s) after discussion at the PhVWP to the CPMP.[5]
Day 120	CPMP	▪ To discuss the report(s) prepared by the specialised expert(s) in the presence of such expert(s) and to agree on the LoQ.
Day 150[6]	Specialised expert(s)	▪ To review the replies prepared by the applicant.
Day 175	Specialised expert(s)	▪ To submit the report(s) to the PhVWP[5]/CPMP, with a copy to the (Co)-Rapporteur and the EMEA.
Day 180[5]	PhVWP[5]	▪ To peer review the report(s) prepared by the specialised expert(s). [5]
Day 180[5]	Specialised expert(s) [5]	▪ To submit the (revised) report(s) after discussion at the PhVWP to the CPMP. [5]
Day 180	CPMP	▪ To discuss the report(s) prepared by the specialised expert(s) in the presence of such expert(s) and to agree on the LoOI.
Day 181	Specialised expert(s)	▪ Where relevant, to attend the oral explanation and to assist the CPMP in the discussions with the applicant.
Day 210	Specialised expert(s)	▪ Where relevant, to attend the CPMP and to assist the CPMP in the finalisation of the CPMP Opinion.

[6] When no need for involvement of specialised expert(s) was identified prior to the LoQ, there is still the possibility to do so at this stage, or at any later stage in the procedure in the light of new information necessitating input of specialised experts. The timetable will have to be adapted accordingly. Sign-of by the EMEA of specialised experts' involvement is needed before such involvement can be initiated.

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London, 5 April 2004
Doc. Ref: EMEA/CPMP/4362/04/Final

Attachment 2

Post-Authorisation Phase: Type II Variation (e.g. Change of the SPC following an USR procedure)

Step of the procedure	Responsible	Task
Day 30	Rapporteur[1]	▪ To decide on the need[2] to involve additional scientific expertise by (1) referring the issue to the PhVWP or (2) involving, in addition to the PhVWP, specialised experts[3]. ▪ When no involvement of additional scientific expertise is needed: - To submit a written report to CPMP Members, including recommendations for regulatory action. ▪ In case of (1): - To request the Rapporteur's PhVWP representative to take the issue forward - To draft, in collaboration with the PhVWP representative, the questions to be addressed by the PhVWP within a specific timeframe. ▪ In case of (2): - To request the Rapporteur's PhVWP representative to take the issue forward. - To identify the specialised expert(s). - To draft, in collaboration with the PhVWP representative, the questions to be addressed by the expert(s) within a specific timeframe.

[1] In specific situations the Co-Rapporteur can be involved in addition to the Rapporteur.
[2] Such need can also be identified by the Co-Rapporteur or any other CPMP Member (or the pharmacovigilance experts involved in the post-authorisation assessment who should put the request to the CPMP Member).
[3] Any involvement of specialised experts can only be initiated once the EMEA has been informed and has signed-of such involvement. The timetable will have to be adapted accordingly.

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Step of the procedure	RESPONSIBLE	Task
Day 50	Specialised expert(s)[4]	▪ To reply to the questions raised and to submit such replies to the Rapporteur's PhVWP representative.
Day 55	Rapporteur's PhVWP representative[4]	▪ To prepare a written report, which includes the replies provided by the specialised expert(s) and to submit such report to the PhVWP, with a copy to the Rapporteur and the EMEA.
Day 60	PhVWP[5,6,3]	▪ Either to address the questions put to the PhVWP and to propose to the CPMP recommendations for regulatory action (scenario (1)) or to peer review the report prepared by the Rapporteur's PhVWP representative, including the replies provided by the specialised expert(s), and to propose to the CPMP recommendations for regulatory action (scenario (2)).
Day 60	Rapporteur's PhVWP representative[5]	▪ To submit the (revised) report to the CPMP and to attend the CPMP (together with specialised expert(s) where applicable).
Day 60[7]	CPMP	▪ To discuss the report and the (PhVWP) recommendations for regulatory action.

[4] In case of involvement of the specialised expert(s), in addition to involvement of the PhVWP.
[5] In case of involvement of the PhVWP.
[6] The PhVWP can also identify the need for involvement of specialised experts. The Rapporteur has to decide on such involvement.
[7] In case of an extension of the 60 day timeframe the timetable will have to be adapted accordingly.