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Conduct of Pharmacovigilance for Centrally Authorised Products

Background information

Discussion of this paper has taken place at the level of the CPMP and the Pharmacovigilance Working Party. This paper was finalised at the Pharmacovigilance Working Party meeting on 8 April 1997 and subsequently adopted by the CPMP at their meeting of 14-17 April 1997.

Following its adoption by the CPMP this paper has been made public.

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I INTRODUCTION

The objective of this paper is to develop a framework whereby all Centrally Authorised Products are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect public health.

The conduct of pharmacovigilance for Centrally Authorised Products rests on obligations and activities placed, through legislation, on a number of parties, i.e. the Member States, the European Commission, the EMEA and the Marketing Authorisation Holders (MAHs). In order to ensure that the obligations are met, it is necessary to clarify the respective responsibilities and roles of the various parties.

This paper presents:

- principles relevant to the conduct of pharmacovigilance for Centrally Authorised Products.
- the functions and procedures for conducting pharmacovigilance for these products.
- the specific roles of the Member States, the CPMP, the Pharmacovigilance Working Party (PhVWP), the (Co)-Rapporteur(s), the EMEA Secretariat, the MAHs and the European Commission, in carrying out functions and procedures for the conduct of pharmacovigilance for Centrally Authorised Products.

II LEGAL FRAMEWORK

- The legal provisions regarding the conduct of pharmacovigilance for Centrally Authorised Products are set out in Chapter 3 of Title II of Council Regulation (EEC) No. 2309/93 of 22 July 1993 and Council Regulation (EC) No 540/95 of 10 March 1995. In particular, Articles 19 to 26 of Chapter 3, of Council Regulation No. 2309/93, place obligations on the MAHs, the Member States and the EMEA.
- Obligations of the MAHs:

  MAHs are obliged to report within 15 days all suspected serious adverse drug reactions (ADRs) occurring within the EU to the Member States in whose territory the incident occurred (Article 22 § 1).

  Furthermore, MAHs have to report all suspected serious unexpected ADRs from outside the EU to the EMEA and the Member States within 15 days (Article 22 § 1).

  MAHs have to submit Periodic Safety Update Reports (PSURs) to the EMEA and the Member States, at least every six months during the first 2 years following authorisation and once a year the following 3 years. Afterwards, in connection with renewal of the Marketing Authorisation, PSURs have to be submitted at 5-yearly intervals (Article 22 § 2).
- Obligations of the Member States:

  In accordance with Article 23, Members States have to report all suspected serious ADRs occurring within their territory to the EMEA within 15 days.
- Obligations of the EMEA:

  Article 20 states that the Agency should receive all relevant information about suspected ADRs for Centrally Authorised Products. In accordance with Article 23, the EMEA must inform the national pharmacovigilance systems of suspected serious ADRs occurring within a Member State.
- The legal provisions regarding supervision and sanctions for Centrally Authorised Products are set out in Chapter 2 of Title II of Council Regulation (EEC) No. 2309/93 of 22 July 1993. In particular, Article 18 of this Chapter provides the basis and the procedures for adoption of Community Decisions following opinions by the CPMP on the measures necessary to ensure the safe and effective use of Centrally Authorised Products.

III PRINCIPLES

The responsibilities and functions of the various partners involved in the Centralised Procedure have been well defined for the co-ordination and evaluation, of Centralised marketing authorisation applications and subsequent variation applications. This framework should also be applied to the conduct of pharmacovigilance for Centrally Authorised Products. As a matter of principle, the handling and analysis of pharmacovigilance data should always be done in close co-operation between the (Co)-Rapporteur(s), the EMEA Secretariat and any Member State(s) who has identified a possible issue.

- The pre-authorisation Rapporteur should take the lead in pharmacovigilance, acting to evaluate all issues relevant to the Centrally Authorised Product. However, there may be situations where the original Rapporteur is not able to fulfil the functions of such evaluation. In such cases the Co-Rapporteur could take this responsibility. If this is not possible, the CPMP would need to appoint another Rapporteur who could take on these responsibilities. In the particular case that one would be confronted with a class-related effect and different Rapporteurs were involved in the pre-authorisation assessment of the various Centrally Authorised Products, the CPMP would need to appoint a "leading" Rapporteur.
- In view of the large number of issues to be handled in the post-authorisation period for Centrally Authorised Products, the Rapporteur will have the responsibility for evaluating and reaching conclusions on these issues in accordance with an agreed timetable, and for determining the issues which need to be considered by PhVWP and CPMP, in close co-operation with the EMEA Secretariat.
- Information relevant to the risks and benefits of Centrally Authorised Products need to be continuously collected in all Member States. Therefore, each Member State plays an important role in collecting information on ADRs and in identifying and evaluating possible alerts of drug safety hazards for Centrally Authorised Products. The scientific expertise of the Member States will be utilised by the Rapporteurs in carrying out pharmacovigilance evaluations. The Rapporteur will generally use the expertise of the Member State from which he originates. However, if considered more appropriate the Rapporteur may work with another Member State, e.g. the Member State which identified the issue under investigation.
- In accordance with current legislation the EMEA Secretariat should collect all information about serious suspected ADRs and distribute this information to the Member States. The role of the EMEA Secretariat, therefore, is one of continuous co-ordination of the Centralised Pharmacovigilance System. The EMEA Secretariat will ensure that MAHs for Centrally Authorised Products adhere to the requirements for safety reporting in accordance with current legislation. Meetings, for MAHs, will be organised at the EMEA at regular intervals in order to provide guidance on ADR reporting to the EMEA. PhVWP will be informed of such meetings in advance and will be given the opportunity to participate.
- The EMEA Secretariat, in close co-operation with the Rapporteur, will inform the CPMP/PhV Working Party of any drug safety hazard concern wherever there is a need for discussion and subsequent action to be taken. It will, in agreement with the Rapporteur, participate in the identification of signals of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects.
- The PhVWP provides a forum for discussion and evaluation of emerging data in order to reach recommendations for consideration by the CPMP. A Drug Monitor for Centrally Authorised Products will be created to track safety issues and will be reviewed at each meeting of the PhVWP. In addition specific issues relating to PSURs, specific obligations, follow-up measures or the need for safety variations may be discussed by the PhVWP at the request of the Rapporteur. At the level of the PhVWP, emerging reports of unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects will be discussed. Furthermore, PSURs are routinely discussed at PhVWP level prior to their consideration by the CPMP.
- The primary responsibility of the MAHs is to assure the safety of their product. Therefore, the MAH is obliged to adhere to the legal provisions as to the spontaneous reporting of ADRs

as well as to the submission of PSURs and other information. Furthermore, issues requiring clarification, further information or specific actions by the MAH need to be clearly presented to the MAH in writing. Such requirements of the MAH should be prepared in collaboration between the Rapporteur, the EMEA Secretariat and any Member State requesting further information, and endorsed where necessary by the CPMP. Meetings with the MAH should involve the Rapporteur, the EMEA Secretariat and others as considered necessary. Minutes of such meetings should be taken and distributed to attendees.

A summary of the role and responsibilities of each of the parties involved in the Centralised Pharmacovigilance System is provided in Annex 1.

IV FUNCTIONS AND PROCEDURES

IV.A Reporting of ADRs for Centrally Authorised Products

1. Pre-Authorisation:

· Once an application for a Marketing Authorisation is submitted to the EMEA, in the pre-authorisation period, information relevant to the benefit/risk evaluation may become available from the applicant, or Member States where the product is already in use on a compassionate basis, or from third countries where the product is already marketed. Since it is essential for this information to be included in the assessment carried out by the (Co)-Rapporteur(s) assessment teams, the applicant is responsible for informing immediately the EMEA Secretariat and the (Co)-Rapporteur(s).

· In the period between the CPMP reaching a final Opinion and the Commission's Decision there need to be procedures in place to deal with information relevant to the benefit/risk of Centrally Authorised Products, which were not known at the time of the Opinion. It is essential for this information to be sent to the EMEA and (Co)-Rapporteur(s) so that it can be rapidly evaluated to an agreed timetable and considered by the CPMP to assess what impact, if any, it may have on the Opinion. The Opinion may need to be amended as a consequence.

2. Post-Authorisation:

· Suspected ADRs related to Centrally Authorised Products are reported directly by health professionals, to each Member State. MAHs report serious suspected ADRs to the Member State in which the reactions occurred, within 15 days of receipt. Each Member State is responsible for following up the single case ADR reports it receives to obtain further information as necessary.

· The Member States should forward to the EMEA Secretariat serious suspected ADRs occurring within their territories.

· The EMEA Secretariat and all Member States should receive directly from the MAHs suspected serious and unexpected ADRs which occur in a country outside of the EU.

· The EMEA Secretariat should ensure that all relevant information about suspected serious unexpected ADRs from outside the EU are entered into the EudraWatch database and Member States should ensure that data on suspected serious ADRs occurring in their territory are uploaded into the EudraWatch database for retrieval e.g. by providing pre-defined reports or allowing for free queries on drug safety profiles. Until the EudraWatch database is available, interim measures will be taken. Each Member State will transmit by E-mail to the EMEA, on a two-weekly cycle, an ASCII file containing CIOMS II line-listings of all serious ADRs received by that Member State (national cases only) for Centrally Authorised Products.

3. Distribution of Information

· Until the EudraWatch database is implemented, the EMEA Secretariat within 24 hours of receipt of ADR line-listings from Member States, will compile a complete line-listing of EU and non-EU ADRs for each Centrally Authorised Product which will be distributed to the relevant Rapporteur and all Member States.

· If cases are considered to be of particular relevance, a Member State may send a complete report directly to the Rapporteur with a copy to the EMEA Secretariat.

· Once EudraWatch is implemented, Member States should be able to access the database electronically to receive ADR data on Centrally Authorised Products.

IV.B Monitoring and Control of Authorisation

1. Signal Generation:

· It is likely that many potential signals will emerge in the early stages of marketing and it will be important for these to be effectively evaluated.

· A signal of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects may be identified by

  - the MAHs
  - the Rapporteur
  - the Member States
  - the EMEA Secretariat in agreement with the Rapporteur

· It is the responsibility of each Member State to identify alerts from information arising in their territory. However, it will be important for the Rapporteur and the EMEA Secretariat to have the totality of information on serious ADRs occurring inside and outside the EU in order to have an overall view of the experience gathered with the concerned Centrally Authorised Product.

· As a matter of routine, the Rapporteur should continually evaluate line-listings of ADRs, in the context of information already available on the product, to determine the emerging ADR profile. Additional information should be requested from the MAH and Member States, as necessary, in liaison with the EMEA Secretariat.

· The Pharmacovigilance Working Party should regularly review the emerging safety issues which will be tracked through the Drug Monitor.

2. Risk Evaluation

· As signals of possible unexpected hazards or changes in the severity, characteristics or frequency of expected adverse effects may emerge from many different sources of data (see above), the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.

· Irrespective of the origin identifying the signal, a risk evaluation should be carried out by

  - the Rapporteur, or
  - the Member State where a signal originated.

· The Rapporteur should work closely with the originator of the alert to evaluate the issues. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or originator Member State, or jointly.

· A Member State other than that of the Rapporteur should not start a full evaluation prior to having contacted the EMEA Secretariat and the Rapporteur, in order to prevent any unnecessary duplication of effort.

3. Periodic Safety Update Reports (PSURs)

- The MAH is required to provide PSURs to all the Member States and the EMEA Secretariat, at 6 monthly intervals post-marketing for the first 2 years, annually for the subsequent 3 years and 5 yearly thereafter. It is the responsibility of the EMEA Secretariat to ensure that the MAH meets these deadlines.
- The MAH should submit any consequential variations simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.
- It is the responsibility of the Rapporteur to evaluate and provide a report in accordance with the agreed timetable and to determine what issues if any need to be referred to the PhVWP and CPMP.
- Actions required following the evaluation of a PSUR will be determined by the Rapporteur and the MAH will be informed by the EMEA Secretariat, after agreement by the CPMP.
- Where changes to the Marketing Authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.

4. Post Authorisation Studies, world literature and other information

- Final and interim reports of MAH sponsored post authorisation studies and any other studies, and other relevant information, may emerge from the MAH, the Member States or other countries at times in between periodic safety updates.
- The Rapporteur should receive and assess any relevant information and provide an assessment report where necessary.
- As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CPMP.
- The actions required following an evaluation will be determined by the Rapporteur and the MAH will be informed by the EMEA Secretariat, after agreement by the CPMP.
- Where changes to the Marketing Authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.
- The MAH should submit any consequential variations simultaneously with the data, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.

5. Post Authorisation Commitments

- It is the responsibility of the EMEA Secretariat to ensure that the MAH meets the deadlines for the fulfilment of specific obligations and follow-up measures, and that the information provided is available to the Rapporteur and to the CPMP.
- The MAH should submit any consequential variations simultaneously with the requested information for the fulfilment of specific obligations/follow-up measures, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.
- For Marketing Authorisations granted under exceptional circumstances, specific obligations will be set out in Annex II.C of the CPMP Opinion. Specific obligations should be reviewed by the Rapporteur, at the interval indicated in the Marketing Authorisation and at the longest annually, and should be subsequently agreed by the CPMP. As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CPMP.
- For Marketing Authorisations granted under exceptional circumstances, the annual review will include a reassessment of the benefit/risk profile. The annual review will in all cases lead to the adoption of an Opinion which will be forwarded to the Commission for preparation of a Decision.

- For all Marketing Authorisations (whether or not the authorisation is granted under exceptional circumstances) follow-up measures may be established, which are annexed to the CPMP Assessment report. These will be reviewed by the Rapporteur, and will be considered by PhVWP and CPMP at the Rapporteur's request.
- Where changes to the Marketing Authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.
- In the case of non-fulfilment of specific obligations or follow-up measures, the CPMP will have to consider the possibility of recommending a variation, suspension, or withdrawal of the Marketing Authorisation, in accordance with the principles laid down in the document "Position Paper on how to proceed with specific obligations and follow-up measures for the management of the marketing authorisation".

IV.C Proceedings in Case of Safety Concerns

1. Hazards in the pre-authorisation phase

- Following the receipt of single case reports or other information relevant to the benefit/risk of a product by the EMEA Secretariat and the (Co)-Rapporteur(s), the latter should assess these pharmacovigilance data. The outcome of the evaluation should be discussed at the CPMP for consideration in the Opinion.
- If pharmacovigilance findings emerge following an Opinion but prior to the Decision, a revised Opinion, if appropriate, should be immediately forwarded to the Commission to be taken into account before preparation of a Decision.

2. Hazards in the post-authorisation phase

A specific tracking system for safety issues relating to Centrally Authorised Products, similar to the present drug monitor will be introduced and reviewed on a regular basis by the PhVWP at their meetings. This summary document will also record relevant actions that have emerged from periodic safety updates, specific obligations, follow-up measures and safety variations.

Following the generation of a signal the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal:

i) Non-urgent safety issues

- Potential concerns that do not fulfil the criteria for a Rapid Alert (see below) should be brought to the attention of the Rapporteur and the EMEA Secretariat only in the first instance.
- Further information may be requested from:
  - other Member States by the originator of the issue using the Infofax system
  - the MAH by the EMEA Secretariat, in agreement with the originator of the issue and the Rapporteur.
- The Rapporteur should work closely with the originator of the alert to evaluate the issues.
- Following evaluation the need for further discussion at the PhVWP and CPMP will be determined by the Rapporteur, and any necessary actions will be agreed by CPMP.
- The EMEA Secretariat is responsible for transmitting the outcome of the evaluation to the MAH.
- However, if deemed necessary, the CPMP should formulate an Opinion on the pharmacovigilance data and forward it to the European Commission accordingly in order to take a Decision.

- These issues will be included in the Drug Monitor for Centrally Authorised Products by the EMEA Secretariat.

ii) Urgent safety issues

- For urgent and serious issues the Rapid Alert System[1] should be used by the Rapporteur, the Member States or the EMEA Secretariat when a signal is detected which leads to concern about the risk/benefit ratio of a Centrally Authorised Product and which could lead to major changes for the status of approval.
- The Rapid Alert should be transmitted to the contact points of the Member States, the EMEA, the European Commission and to the Rapporteur of the Centrally Authorised Product which is the subject of the alert.
- The EMEA Secretariat, in agreement with the Rapporteur, should promptly start an inquiry and information exchange with the MAH(s).
- The EMEA Secretariat will co-ordinate the process.
- The Rapporteur should work closely with the originator of the alert to evaluate the issues. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or originator Member State, or jointly.
- Following risk evaluation a discussion should be held at the PhVWP and subsequently at the CPMP within a defined timeframe.
- Any resulting CPMP Opinion on the measures to ensure the safe and effective use of the Centrally Authorised Product will be transmitted by the EMEA Secretariat to the European Commission, in order to take a Decision.
- In some cases immediate action is essential to protect public health. In such cases the basic steps outlined above need to be followed, but within a much shorter time-frame, with the involvement of PhVWP and CPMP at a much earlier stage, and with particular mechanisms in place to provide a CPMP Opinion and Commission Decision rapidly. Rapid actions will need to be co-ordinated across all Member States, however in some situations one or a number of Member States may consider it necessary to take immediate suspensive action before such co-ordinated action occurs.

  – Crisis Management:

  - Following detection of an urgent safety hazard which could have a serious impact on public health, immediate action needs to be taken to evaluate and consider the options and timescale for action. A Crisis Management Plan, agreed with the CPMP, will be implemented by the EMEA Secretariat in close consultation with the European Commission.

  – Action taken by a Member State:

  - Upon detection of a safety hazard where urgent action is deemed essential to protect human health, a Member State may suspend the use of a medicinal product on its territory.
  - The Member State must inform the EMEA, the European Commission and other Member States no later than the following working day of the reasons for its action. The Rapid Alert System1 should be used for this purpose.
  - The European Commission will request the opinion of the EMEA within a time frame which it shall determine depending on the urgency of the matter. In that respect two possible procedures can be envisaged for implementation by the EMEA Secretariat depending on the time frame:

[1] Rapid Alert System (RAS) as described in Note for Guidance on RAS in Pharmacovigilance (CPMP/PhVWP/005/96)

- the first procedure is described in the Crisis Management Plan
- the second is the convening of an extraordinary CPMP by the Executive Director of the EMEA, after consultation with the CPMP Chairperson, in order to provide the European Commission with a recommendation on the suspensive measures.

IV.D Statements to Health Professionals and the Public

Health professionals and, if considered appropriate, the public need to be informed about safety issues relevant to Centrally Authorised Products, in addition to the information provided in product information. It is important that consistent information is provided in all Member States. If there is such a requirement the Rapporteur should propose the content of information for consideration by the PhVWP and subsequent discussion and adoption by the CPMP. The agreed information may be distributed in Member States by letters from the MAH or Member States authorities or through Member States' authorities' bulletins. In some cases co-ordinated press releases, in addition to the CPMP press release, may be necessary. The text and timing for release of such information should be agreed by all parties prior to their despatch.

IV.E Advertising (Subject to further discussion within the Pharmaceutical Committee)

Council Directive 92/28/EEC lays down the legislative base for the control of advertising medicinal products. Because company marketing strategies for Centrally Authorised Products may be similar across the EU, consideration should be given to what interactions should take place between Member States in the event of an important advertising concern with potential public health implications occurring with a Centrally Authorised Product. The EMEA and the Rapporteur should be informed by the Member States of such concerns. The PhVWP may be an appropriate forum to discuss such issues in order to ensure that when it is considered that a company is making misleading claims with safety implications in several Member States, consistent action is taken whenever possible. The CPMP should be informed subsequently.

ANNEX I

SUMMARY OF THE ROLE AND THE RESPONSIBILITIES OF ALL PARTNERS INVOLVED IN THE CONDUCT OF PHARMACOVIGILANCE FOR CENTRALLY AUTHORISED PRODUCTS

Marketing Authorisation Holder	· Establish and maintain a system, accessible at a single point in the EU, to collect, collate, and evaluate pharmacovigilance data · Meet legal obligations for reporting suspected adverse drug reactions · Meet legal obligations regarding the preparation and the submission of PSURs · Respond fully to requests from authorities for additional information necessary for the evaluation of the benefits and risks of a medicinal product · Ensure the Marketing Authorisation is maintained and reflects the latest information
Member States	· Have in place national pharmacovigilance systems · Inform the European Commission, the CPMP, the EMEA, the Member States and the MAHs of any relevant actions · Collect and collate risk/benefit data · Provide serious ADRs received in its territory to the EMEA and the relevant MAH within 15 days of receipt · Identify and evaluate drug safety alerts and conduct risk/benefit evaluations · Provide representation on CPMP, PhVWP and Rapporteurs/Co-Rapporteurs · Implement Commission Decisions · In case of urgent action to protect public health, suspend the use of the product in the Member State's territory and inform, in accordance with the legislation, the EMEA and the European Commission of the basis for action
EMEA Secretariat	· Co-ordination of the Centralised Pharmacovigilance System · Monitor the legal obligations of the MAHs · Receipt of serious ADRs and provision to the Member States and the Rapporteur · In agreement with the Rapporteur, identify signals of possible unexpected hazards or changes in expected adverse effects · In agreement with the Rapporteur, inform all involved parties of any safety hazard concern

	· Co-ordination of the evaluation of data by the Rapporteurs and consideration by the CPMP to reach Opinions · Communication of Opinions to the European Commission · Communication with the MAH on all relevant issues in consultation with the Rapporteur · Maintenance of the Crisis Management System for Centrally Authorised Products
Rapporteur	· Responsible for evaluating all risk/benefit issues for Centrally Authorised Products · Regularly evaluate ADRs and other risk/benefit data on receipt, PSURs, company reports and variation applications to agreed timetables, obtaining additional information from the MAH and the Member States as necessary · Provide risk-benefit assessment reports to agreed timetables for consideration by the PhVWP and CPMP as necessary, with proposals on appropriate remedial action
Pharmacovigilance Working Party	· Regularly review Drug Monitor of safety issues for Centrally Authorised Products · Discussion of emerging drug safety issues at the request of the Rapporteur · Discussion of PSURs at the request of the Rapporteur · Recommendations to the CPMP on risk/benefit evaluations and actions necessary to minimise risk and maximise benefit
CPMP	· Discussion of the risk/benefit on the basis of the Rapporteur's assessment report · Formulation of Opinions
European Commission	· Competent Authority for Centrally Authorised Products · Formulation of Decisions · Enforcement of legislative requirements and enforcement of the implementation of Decisions by Member States and MAHs