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

London, 15 November 2001
CPMP/PhVWP/1618/01

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**POSITION PAPER ON COMPLIANCE WITH
PHARMACOVIGILANCE REGULATORY OBLIGATIONS**

DISCUSSION IN THE PHARMACOVIGILANCE WORKING PARTY	March 2001
TRANSMISSION TO CPMP	March 2001
RELEASE FOR CONSULTATION	June 2001
DEADLINE FOR COMMENTS	September 2001
DISCUSSION OF COMMENTS BY THE PHARMACOVIGILANCE WORKING PARTY	October 2001
ADOPTION BY CPMP	November 2001
DATE OF COMING INTO OPERATION	January 2002

Note:

The first version of this document was developed by the CPMP Pharmacovigilance Working Party (PhVWP), following consultation with the EMA and national Competent Authorities through the PhVWP Members, including consultation with Good Clinical Practice and Good Manufacturing Practice Inspectorates. It was adopted by the CPMP in May 2001 and endorsed by the Heads of Agencies at their meeting in June 2001. This version was agreed by the PhVWP in October 2001 and adopted by the CPMP in November 2001, taking into account comments received from interested parties during the consultation phase. It was endorsed by the Heads of Agencies at their meeting in November 2001 for coming into operation in January 2002.

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1 INTRODUCTION

The rapid and effective identification and assessment of drug safety issues is dependent on early access to complete information. This is fundamental to Competent Authorities and Marketing Authorisation Holders (MAHs) ability to protect public health in taking appropriate action swiftly. Competent Authorities have an obligation to implement medicines legislation and non-compliance with pharmacovigilance regulatory obligations could have a potentially serious public health impact.

This paper, produced by the Pharmacovigilance Working Party (PhVWP) of the Committee for Proprietary Medicinal Products (CPMP), sets out the legal basis for pharmacovigilance obligations, how compliance should be monitored in the European Union (EU) and the types of regulatory action which may be considered in the event of non-compliance.

2 LEGAL BASIS OF PHARMACOVIGILANCE

The pharmacovigilance regulatory obligations placed on MAHs are laid down in Council Regulation EEC 2309/93 (Title 2, Chapter 3), Council Directive 75/319/EEC (Chapter 5a) and Commission Regulation EC 540/95. The legal basis for pharmacovigilance inspections at a National level is laid down in Chapter V, Article 26 of 75/319/EEC.

Pharmacovigilance guidelines have been provided in Notice to Marketing Authorisation Holders and will be published in Volume IX of *The Rules Governing Medicinal Products In The EU*.

The MAHs should ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility for their products on the market and to ensure that appropriate action can be taken, when necessary. This includes the MAH having at its disposal continuously at least one appropriately qualified person responsible for pharmacovigilance available at all times within the European Economic Area (EEA), and the establishment of a system for the collection, preparation and submission of expedited adverse drug reactions (ADR) and periodic safety update reports to competent authorities.

Pharmacovigilance regulatory obligations are placed on all MAHs. The obligations are the same whether the MAH is an innovative pharmaceutical company, or a generic company.

3 MONITORING COMPLIANCE

EU Competent Authorities have been working for many years to facilitate MAHs in meeting pharmacovigilance regulatory obligations. This has included the development of guidelines, education programmes, responding to enquiries and the development of electronic reporting. Competent Authorities should monitor MAHs for compliance with pharmacovigilance regulatory obligations. Furthermore, Competent Authorities shall exchange information in cases of non-compliance and will take appropriate regulatory action as required. It should be noted that enforcement action is within the competency of individual Member States.

4 SYSTEM REQUIREMENTS AND NON-COMPLIANCE

Set out below is an outline of how compliance monitoring should be performed:

4.1 System requirements

All MAHs must have an appropriate system of pharmacovigilance in place. This system should be capable of the following:

- Expedited reporting
- Periodic safety update reporting
- Responding to requests for information from Competent Authorities
- Handling of urgent safety restrictions and safety variations
- Continuous monitoring of the safety profile of the authorised medicinal products and notifying competent authorities and health professionals of changes to the benefit / risk of products
- Meeting CPMP commitments (where MAHs hold a centralised marketing authorisation)
- Internal audit of the pharmacovigilance system.

Pharmacovigilance data should be collated, and be accessible, at least at one point within the EEA.

Competent authorities will ensure that a system of pharmacovigilance is in place within MAHs through scrutiny of standard operating procedures and pharmacovigilance inspections (see section 5 below).

At the time of assessment of Marketing Authorisation Applications, Competent Authorities will consider requesting documentation demonstrating that a system of pharmacovigilance is in place.

4.2 Qualified Person Responsible for Pharmacovigilance

EU law requires all MAHs to have at least one qualified person responsible for pharmacovigilance within the EEA. This person must be permanently and continuously at the disposal of the MAH or a clearly identified and appropriately qualified deputy must be available. National regulations in some Member States require a nominated individual in that country who has specific legal obligations in respect of pharmacovigilance at a national level.

Competent Authorities will compile a list of qualified persons responsible for pharmacovigilance within the EEA. This list will include contact names and business addresses, telephone and fax numbers (including out of hours). This list will be kept up to date.

4.3 Change in benefit / risk

One of the key responsibilities of MAHs is to immediately notify Competent Authorities of any change in the balance of risks and benefits of their products. Any failure to do so may pose a significant threat to public health. Any evidence of failure to notify such changes will result in consideration of enforcement action by Competent Authorities.

4.4 Expedited ADR reporting

Reports of adverse drug reactions (ADRs) meeting the expedited reporting requirements should be submitted to the Competent Authority within fifteen calendar days of receipt by the MAH. The date of receipt by the MAH should be clearly recorded on all expedited reports. If a reaction is spontaneously reported by a healthcare professional, this implies the reporter has judged, at least a possible causal association. Detailed guidance on expedited reporting is given in Notice to Marketing Authorisation Holders and will be published in Volume IX of the *Rules Governing Medicinal Products in the EU*. Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 15 days) and submission of reports of poor quality (particularly where evidence suggests that this results from inadequate company follow-up of individual cases).

Methods employed to prospectively monitor compliance with expedited ADR reporting may include the following:

- Monitoring ADR reports received against a complete list of MAs or MAHs to determine complete failure to report
- Monitoring the time between receipt by MAH and submission to Competent Authorities to detect late reporting
- Monitoring the quality of reports, including comparison of the quality of duplicate reports (where a report has been received by the Competent Authorities directly from a healthcare professional and indirectly via the MAH). Submission of reports judged to be of poor quality may result in the follow-up procedures of MAHs being scrutinised.
- Checking Periodic Safety Update Reports (PSURs) to ensure all qualifying serious reports have been expedited
- Checking interim and final reports of post-authorisation studies to ensure all qualifying serious reports have been expedited.
- At inspection, review a sample of reports on the MAH database to: assess quality of data, determine whether the relevant reports have been expedited and are included on the database of the Competent Authority and check systems are in place to follow-up reports.

4.5 Periodic Safety Update Reports (PSURs)

PSURs are important pharmacovigilance documents. They provide an opportunity for MAHs to review the safety profile of their products and ensure that the Summary of Product Characteristics and Patient Information Leaflet are up to date. They also provide Competent Authorities with a valuable source of pharmacovigilance data. For these reasons Competent Authorities place great importance on compliance with periodic reporting. Non-compliance may include:

- Submission: complete non-submission of PSURs, submission outside the correct cycle or outside the correct time frames (without previous submission of a type II variation), non-restart of the cycle of submission when necessary
- Format of the document: report not in accordance with Notice to Marketing Authorisation Holders
- Concealment of information particularly in the following sections of the report: Update of Regulatory Authority or MAH Actions taken for Safety Reasons, Changes to Reference Safety Information, Patient Exposure, Presentation of Individual Case Histories
- Poor quality reports: poor documentation of adverse drug reaction reports or insufficient information provided to perform a thorough assessment in the Presentation of Individual Case Histories section, new safety signals not or poorly assessed in the Overall Safety Information section, misuse not highlighted, absence of standardised medical terminology (e.g. MedDRA)
- Company core data sheet (CCDS): where changes have been made to the CCDS since the submission of the last PSUR, submission of a report where the covering letter does not highlight the differences between the CCDS and the EU or National SPCs
- Previous requests from Competent Authorities not addressed: submission of a report where previous requests from Competent Authorities have not been addressed (e.g. close monitoring of specific safety issues).

4.6 Requests for information from the competent authorities

No fixed time frames are laid down in EU legislation or guidelines for responding to a request for information from Competent Authorities. This reflects the fact that the appropriate time frame will depend on the urgency of the pharmacovigilance issue and its potential impact on public health. Despite this, Competent Authorities will ensure that all requests for information from MAHs have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. Competent Authorities will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to provide the necessary information/data within the deadline may be considered as non-compliance.

4.7 Submission of safety variations

EU legislation and guidelines do not specify deadlines for submission of safety variation applications. As with responding to requests for information from Competent Authorities, deadlines for submission of safety variations will depend on the urgency and potential public health impact of the pharmacovigilance issue. Competent Authorities will ensure that requests for safety variations have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. Competent Authorities will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to submit the variation application within the deadline may be considered as non-compliance.

4.8 CPMP commitments in respect of centrally authorised medicines

EU legislation and guidelines do not specify deadlines for the submission of Follow-up measures following the granting of a centralised Marketing Authorisation. The timeframe for submission of Follow-up Measures should be clearly stated in a letter of undertaking signed by the applicant at the time of the CPMP Opinion.

Concerning Specific Obligations, pursuant to article 13 (2) of Council Regulation (EEC) No 2309/93 and according to Part 4G of the Annex to Council Directive 75/318/EEC, the applicant must complete an identified programme of studies within a time period specified by the Competent Authority, the results of which shall form the basis of a reassessment of the benefit/risk profile. An expert report addressing the overall benefit/risk profile of the product should be submitted at least 2 months before each annual reassessment to be included in the revised CPMP assessment report.

Non-compliance may include:

- Complete non-submission of data, including non submission of specific obligations before the annual re-assessment
- Submission of data after the deadline agreed in the letter of undertaking from the Company (without previous agreement from the Competent Authority)
- Poor quality of a report requested as a Follow-up Measure or Specific Obligation.

4.9 Post-authorisation safety studies

Because of the objectives of safety studies there is considerable potential for safety signals to arise or changes in the balance of benefits and risks of products to be identified. Therefore, expedited reporting of relevant ADRs and submission to Competent Authorities of interim and final study reports from such studies has an important role in protecting public health. Where appropriate, Competent Authorities will scrutinise protocols prior to initiation of safety studies. For studies to be conducted in more than one Member State, it may be appropriate for protocols to be considered by the CPMP Pharmacovigilance Working Party. Competent Authorities should check that relevant ADR reports are expedited from safety studies and will monitor the submission of interim and final study reports.

5 PHARMACOVIGILANCE INSPECTIONS

To ensure that MAHs comply with pharmacovigilance regulatory obligations and to facilitate compliance, Competent Authorities may conduct pharmacovigilance inspections. There should be collaboration between Competent Authorities to minimise duplication and maximise coverage. Inspections will be random and systematic, as well as targeted to MAHs suspected of being non-compliant. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action.

6 REGULATORY ACTION

Under EU legislation, to protect public health, Competent Authorities are obliged to implement medicines' legislation and to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance regulatory obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of non-compliance but any instance of non-compliance may be referred for enforcement action.

In the event of non-compliance, regulatory options include the following:

- Education and Facilitation
MAHs may be informed of non-compliance and advised on how this can be remedied.
- Inspection
Non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.
- Warning
Competent Authorities may issue a formal warning reminding MAHs of their pharmacovigilance regulatory obligations.
- Naming non-compliant MAHs
Competent Authorities will consider a policy of making public a list of MAHs found to be seriously or persistently non-compliant.
- Formal caution
A formal caution will be considered if the non-compliant MAH has admitted a criminal offence has occurred.
- Prosecution
Cases of serious or persistent non-compliance may be prosecuted. In addition to a prosecution of the MAH this action may also be taken against directors, managers or the Qualified Person responsible for pharmacovigilance.

Evidence of failure to notify a change in the balance of benefits and risks of a product, deliberate non-compliance or a failure to improve systems after the identification of non-compliance would be considered as examples of serious non-compliance.

7 CONCLUSIONS

This document has set out the EU Competent Authorities position with respect to compliance with pharmacovigilance regulatory obligations. This document will be made publicly available and will be updated if there is a significant change in policy in this area.