

**GUIDELINE ON MONITORING OF COMPLIANCE WITH
PHARMACOVIGILANCE REGULATORY OBLIGATIONS AND
PHARMACOVIGILANCE INSPECTIONS**

(INCORPORATES GUIDANCE ON THE DETAILED DESCRIPTION OF THE MAH'S
PHARMACOVIGILANCE SYSTEM TO BE INCLUDED IN THE MARKETING AUTHORISATION
APPLICATION)

**THIS GUIDELINE WILL BE INCORPORATED IN VOLUME 9 OF EUDRALEX
AFTER THE CONSULTATION PROCESS**

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1. EXECUTIVE SUMMARY

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 or animal 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 or animal health impact.

This guideline sets out the framework for implementation, in the context of the revised pharmaceutical legislation, of the monitoring of compliance with pharmacovigilance obligations and pharmacovigilance inspections. In the same context it sets out the information to be supplied in the Marketing Authorisation Application (MAA) giving a detailed description of the pharmacovigilance system of the MAH and proof that the MAH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of adverse reactions. The guideline is applicable for any medicinal product, whatever the marketing authorisation procedure used. The inspection process described focuses on Centrally Authorised Products (CAPs), however the principles may be generally applicable.

The legislation requires that a "detailed description of the pharmacovigilance and, where appropriate, of the risk-management system...." should be included within the application for a marketing authorization. The description of the risk management system, which includes the product specific pharmacovigilance activity, is not addressed in this guideline (for medicinal products for human use it is the topic of a separate guideline (EMEA/CHMP/96268/2005)).

The pharmacovigilance regulatory obligations placed on MAHs are laid down in Regulation (EC) No 726/2004 of the European Parliament and the Council, and Directives 2001/82/EC and 2001/83/EC of the European Parliament and the Council as amended. Guidelines on the interpretation of legislative pharmacovigilance requirements are published in Volume 9 of The Rules Governing Medicinal Products In The European Union.

2. INTRODUCTION (BACKGROUND)

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 or animal 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 or animal health impact.

3. SCOPE

This guideline sets out the framework for implementation, in the context of the revised pharmaceutical legislation, of the monitoring of compliance with pharmacovigilance obligations and pharmacovigilance inspections. In the same context it sets out the information to be supplied in the Marketing Authorisation Application (MAA) giving a detailed description of the pharmacovigilance system of the MAH and proof that the MAH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of adverse reactions. The guideline is applicable for any medicinal product, whatever the marketing authorisation procedure used. The inspection process described focuses on CAPs, however the principles may be generally applicable.

The description of the risk management system, which includes the product specific pharmacovigilance activity, is not addressed in this guideline (for medicinal products for human use it is the topic of a separate guideline (EMA/CHMP/96268/2005)).

4. LEGAL BASIS

The pharmacovigilance regulatory obligations placed on MAHs are laid down in Regulation (EC) No 726/2004, and Directives 2001/82/EC and 2001/83/EC as amended. Guidelines on the interpretation of legislative pharmacovigilance requirements are published in Volume 9 of The Rules Governing Medicinal Products In The European Union.

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 permanently and continuously an appropriately qualified person responsible for pharmacovigilance residing within the European Economic Area, and the establishment of a system for the collection, preparation and submission of all suspected adverse reactions that need to be reported promptly or at the latest within 15 days, hereafter referred to as expedited adverse reaction reports (elsewhere also referred to as expedited Individual Case Safety Reports (ICSRs)), reports of any transmission of an infectious agent in a third country, Periodic Safety Update Reports (PSURs) and other relevant information to competent authorities. The submission of expedited adverse reaction reports is to be done electronically.

Pharmacovigilance regulatory obligations are placed on all MAHs. The obligations are the same independent of the legal basis for the submission of the application.

4.1 Roles of the Agency

The roles of the Agency are set out in Regulation (EC) No 726/2004 and in Volume 9 of The Rules Governing Medicinal Products In The European Union. Regarding the monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections, Article 57(1)(c) of Regulation (EC) No 726/2004 states “coordination of the supervision, under practical conditions of use, of medicinal products which have been authorized within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation;” and article 57(1)(i) of Regulation (EC) No 726/2004 states “coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations”, are of particular relevance.

4.2 Roles of the national competent authorities

The roles of the national competent authorities are set out in Directive 2001/83/EC and Directive 2001/82/EC, in Regulation (EC) No 726/2004, and in Volume 9 of The Rules Governing Medicinal Products In The European Union.

With respect to medicinal products for human use Title IX of Directive 2001/83/EC sets out requirements for pharmacovigilance. Articles 101, 102 and 102(a) of Directive 2001/83/EC require Member States to take all appropriate measures to encourage reporting of suspected adverse reactions to them by health care professionals, provide powers to impose specific requirements in this respect and require the operation of a pharmacovigilance system by the Member States and communication of reports to other Member States and the Agency. Provisions are made regarding the independence of the funding of the pharmacovigilance activities, communication networks and market surveillance. Article 104.9 establishes a basis for penalties where MAHs fail to discharge their obligations. Article 105 provides for the establishment of a data-processing network and the monitoring of compliance with expedited reporting requirements.

With respect to veterinary medicinal products Title VII of Directive 2001/82/EC sets out requirements for pharmacovigilance. Articles 72, 73 and 73(a) of Directive 2001/82/EC require Member States to take all appropriate measures to encourage reporting of suspected adverse reactions to them by health care professionals, provide powers to impose specific requirements in this respect and require the operation of a pharmacovigilance system by the Member States and communication of reports to other Member States and the Agency. Provisions are made regarding the independence of the funding of the pharmacovigilance activities, communication networks and market surveillance. Article 75.8 establishes a basis for penalties where MAHs fail to discharge their obligations. Article 77 provides for the establishment of a data-processing network and the monitoring of compliance with expedited reporting requirements.

Article 84 of Regulation (EC) 726/2004 sets out the roles of the Member States, the Agency and the Commission with respect to the imposition of penalties for infringement of that Regulation or regulations adopted pursuant to it.

In addition items specific to inspection are addressed in section 4.3, below.

4.3 Pharmacovigilance Inspections

The legal basis for the conduct of Pharmacovigilance inspections is set out in article 111 of Directive 2001/83/EC on medicinal products for human use and article 80 of Directive 2001/82/EC on medicinal products for veterinary use, and in article 19(1) of Regulation (EC) 726/2004 (human products) and 44.1 (veterinary products).

4.4 Detailed description of the pharmacovigilance system to be included in the MAA

The applicant for a Marketing Authorisation (MA) is required (article 8(3)(ia) of Directive 2001/83/EC and article 12(3)(k) of Directive 2001/82/EC) to provide a detailed description of the system of pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce. This guideline addresses the general description of the pharmacovigilance system (see chapter 5). The description of the risk management system, which includes the product specific pharmacovigilance activity, is not addressed in this guideline (for medicinal products for human use it is the topic of a separate guideline (EMEA/CHMP/96268/2005)).

4.5 Proof, of the services of a qualified person responsible for pharmacovigilance and of the necessary means to notify adverse reactions, to be included in the MAA

The applicant is required (article 8(3)(n) of Directive 2001/83/EC and article 12(3)(o) of Directive 2001/82/EC) to provide proof that they have the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

5 DETAILED DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEM TO BE INCLUDED IN THE MARKETING AUTHORISATION APPLICATION AND PROOF THAT THE APPLICANT HAS THE

SERVICES OF A QUALIFIED PERSON AND THE NECESSARY MEANS FOR THE NOTIFICATION OF ADVERSE REACTIONS

5.1 *Statement of the MAH and the qualified person regarding their availability and the means for the notification of adverse reactions*

A signed statement from the MAH and the Qualified Person to the effect that the applicant has their services available as qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction occurring either in the Community or in a third country should be provided in Module 1/Part 1 of the MAA. This statement may make reference to the detailed description of the pharmacovigilance system (see 5.3) and indicate what is already in place, and confirm which items will be put in place before the product is placed on the market in the Community.

5.2 *Location of the description in the MAA*

The detailed description of the pharmacovigilance system should be provided in Module 1/Part 1 of the MAA.

5.3 *Elements of the Pharmacovigilance system that should be described in the Marketing Authorisation Application.*

All MAHs must have an appropriate system of pharmacovigilance in place. The detailed description of the pharmacovigilance system should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation, should be added:

5.3.1 Qualified Person Responsible for Pharmacovigilance

- The name, address (es), contact details of the Qualified Person responsible for pharmacovigilance, located in the EEA
 - The Curriculum Vitae of the Qualified Person Responsible for Pharmacovigilance and a description of the back-up procedure to apply in their absence, including the information relevant to their role (qualifications, training and experience).
 - The job description of the Qualified Person Responsible for Pharmacovigilance.

5.3.2 Organisation

- The names and addresses of the organisations and locations where EEA and global pharmacovigilance activities are undertaken. In particular those sites where databases are located, where individual case reports and periodic safety update reports are prepared, reviewed (including where medical review takes place) and processed for reporting to the Competent Authorities.
- Identification of the point(s) in the Community at which pharmacovigilance data is accessible.
- Organisation chart(s) providing an overview of the global and EEA pharmacovigilance units, illustrating the relationships between them, with affiliate/parent companies, licensing partners and contractors. The chart(s) should show the reporting relationships with management and clearly show the position of the EEA Qualified Person within the organisation. Individual names of people should not be included here. Links with other departments involved in pharmacovigilance activities should be indicated (e.g. regulatory affairs, medical information,

sales and marketing, clinical research, product quality, quality assurance audit (for pharmacovigilance), and information technology supporting pharmacovigilance database(s).

- A brief summary of the pharmacovigilance activities undertaken by each of the units involved.
- Flow diagrams indicating the flow of safety reports of different origins and types obtained and transmitted. These should indicate how reports/information is processed and reported from the source to the point of receipt by the Competent Authorities and, where appropriate, to healthcare providers.
- A brief description of archiving activities for pharmacovigilance activities, location and responsibility for these.
- A brief description of the responsibilities for quality assurance auditing of the company's pharmacovigilance systems.

5.3.3 Procedures in place, which are documented in writing

- A list of the written policies and procedures describing the pharmacovigilance activities of the company. These need not be separate titles but the list should indicate which procedures cover the following activities:
 - The activities of the Qualified Person
 - The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of individual case reports
 - Reports of different origin should be addressed:
 - EEA and third countries
 - Healthcare professionals
 - Other persons, such as animal owners or handlers
 - Sales and marketing personnel, and other MAH personnel
 - Licensing partners
 - Regulatory authorities
 - Literature
 - Clinical trials
 - Compassionate use (for human medicinal products)
 - Patients
 - Other
 - The follow-up of these reports for missing information and for information on the progress and outcome of the case
 - Detection of duplicate reports

- The reporting, including expedited and electronic reporting, of individual case safety reports (ICSRs)
 - The preparation, processing, quality control, review (including medical review) and reporting of Periodic Safety Update Reports
 - Continuous monitoring of the safety profile of the authorised medicinal products and notifying competent authorities and healthcare professionals of changes to the risk-benefit balance of products
 - Signal generation and review
 - Risk-benefit assessment
 - Responses to requests for information from Regulatory authorities
 - Database or other record system
 - Handling of urgent safety restrictions and safety variations
 - Meeting CXMP commitments in relation to a centralised marketing authorisation
 - The procedures covering Risk Management (where a specific Risk Management System, in addition to routine pharmacovigilance, is required (see also EMEA/CHMP/96268/2005 for medicinal products for human use))
 - Internal audit of the pharmacovigilance system
 - Staff Training
 - Maintenance and update of the Pharmacovigilance Planning (for medicinal products for human use see EMEA/CHMP/96268/2005)
- Copies of the procedures should be available within two working days on request by the Competent Authorities

All information received by the MAH should be managed in order to respect the confidentiality of patients and reporters.

5.3.4 Databases

A listing of the databases used for pharmacovigilance purposes and brief functional descriptions including:

- Database software system description including the name, version details, and details of the sites using each system. Where multiple systems or locations are used, the links between them should be shown. These descriptions should be diagrammatic where possible.
- For each system the name of the commercial vendor or developer, or indication of the development (e.g. in-house). Indicate whether the system was customised or off the shelf.
- For each system a brief functional description and also a brief description of the relationships between multiple systems and their overall functionality.
- A statement of compliance of the system with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in part III (for medicinal

products for human use) of Volume 9 of The Rules Governing Medicinal Products In The European Union.

- A copy of the registration with the EudraVigilance system and identification of the process/system used for electronic reporting to the competent authorities.
- A statement about the validation status of each system, and of connections between multiple systems.
- List of legacy systems used, relevant to the medicinal product in question.
- Identification of the responsibilities from an IT perspective and from an operational perspective for each system (this should allow ready identification with the elements of the organisation and locations described under 5.3.2).

5.3.5 Links with other organisations

Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities:

- Provide a brief description of the agreements with co-marketing partners and contractors for pharmacovigilance activities; include reporting responsibilities and arrangements for literature searches.

5.3.6 Training

Staff should be appropriately trained for performing pharmacovigilance related activities. Provide a brief description of the training system and indicate where the training records, CVs and job descriptions can be found.

5.3.7 Documentation

Provide a brief description of the locations of the different types of pharmacovigilance source documents. Reference can be made to the organisation charts described under 5.3.2

5.3.8 Quality Management system

Provide a brief description of the Quality management system, making cross-reference to the elements provided under the above sections. Particular emphasis should be placed on organisational roles and responsibilities for the activities and documentation, and for ensuring corrective and preventive action.

6 MONITORING OF COMPLIANCE

6.1 *Monitoring, by the competent authorities, of Compliance*

EEA 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. Article 84 of Regulation (EC) 726/2004 sets out the roles of the Member States, the Agency and the Commission with respect to the imposition of penalties for infringement of that Regulation or regulations adopted pursuant to it.

Set out below is an outline of how compliance monitoring should be performed. In this context compliance monitoring is in addition to inspection activities and may be carried out separately from them or as a prelude or follow-up to inspection. Where compliance monitoring raises concerns these should be highlighted to the competent authorities and in the case of CAPs, to the EMEA, Rapporteur/Co-Rapporteur, CXMP, their respective Pharmacovigilance Working Parties and the competent authority (ies) concerned. Deficiencies identified during compliance monitoring may lead to an inspection request.

Competent authorities will ensure that a system of pharmacovigilance is in place within MAHs through scrutiny of documented procedures, safety reports and pharmacovigilance inspections (see sections 3, 4 and 5).

6.2 Qualified Person Responsible for Pharmacovigilance

EU legislation requires all MAHs to have a qualified person responsible for pharmacovigilance within the Community. This person must be permanently and continuously at the disposal of the MAH. 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 maintain 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).

6.3 Availability of pharmacovigilance data

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

6.4 Change in the evaluation of the risk-benefit balance of a product

One of the key responsibilities of MAHs is to immediately notify the 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 or animal health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the competent authorities.

6.5 Expedited adverse reaction reporting

Reports of suspected adverse reactions meeting the expedited reporting requirements should be submitted to the relevant competent authority (ies) 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 Volume 9 of The Rules Governing Medicinal Products In The European Union. 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). Failure to comply with electronic reporting requirements will be monitored.

Methods available to regulatory authorities for prospective monitoring of compliance with expedited reporting of adverse reactions could be:

- Monitoring adverse reaction 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. 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 detect under-reporting (e.g. of expedited reports).
- Checking interim and final reports of post-authorisation studies to ensure that all qualifying serious reports have been submitted within 15 days.

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 EudraVigilance database, and check systems are in place to follow-up reports.

6.6 *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 Package Leaflet are up to date. They also provide the competent authorities with a valuable source of pharmacovigilance data. For these reasons the competent authorities place great importance on compliance with periodic reporting. Non-compliance may include:

- Non-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.
- Incorrect format of the document: report not in accordance with Notice to Marketing Authorisation Holders contained in Volume 9 of The Rules Governing Medicinal Products In The European Union.
- 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 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/VEDDRA).
- Company core data sheet (CCDS) or Summary of Product Characteristics (SPC): where changes have been made to the CCDS or SPC since the submission of the last PSUR, for human medicinal products - the covering letter does not highlight the differences between the CCDS and the EU SPC.

Previous requests from regulatory 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).

6.7 *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 mainly on the urgency of the pharmacovigilance issue and its potential impact on public or animal health. The 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.

6.8 *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 or animal health impact of the pharmacovigilance issue. The 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. The 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.

6.9 *CXMP commitments in respect of CAPs*

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 CXMP Opinion.

Regulation (EC) No 726/2004 foresees a number of particular possibilities for Marketing Authorisations and post marketing activities. Compliance with the provisions of these measures will be monitored. These include:

- Conditional Marketing Authorisations
- Marketing Authorisations under Exceptional Circumstances

and the Specific Obligations or Follow-up measures as applicable to these. Normal Marketing Authorisations may also include Follow-up Measures.

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).
- Failure to implement a Specific Obligation.
- Failure to implement a Follow-up Measure.
- Poor quality of a report requested as a Follow-up Measure.
- Poor quality of a report requested as a Specific Obligation.
- Failure to implement an urgent provisional measure.

6.10 *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 risks and benefits of products to be identified. Therefore, expedited reporting of relevant adverse drug reactions (ADRs) and submission to competent authorities of interim and final study reports from such studies has an important role in protecting public or animal health. Where appropriate, competent authorities will scrutinise protocols prior to initiation of safety studies. Competent authorities should check that relevant ADR reports are expedited from safety studies and will monitor the submission of interim and final study reports. Further guidance on this issue is available in Volume 9 of The Rules Governing Medicinal Products In The European Union.

6.11 *Risk Management and product specific pharmacovigilance activity are not the topic of this guideline (addressed in a separate Guideline for medicinal products for human use EMEA/CHMP/96268/2005).*

7. 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. The scheduling and conduct of these inspections will be driven by risk analysis criteria. The inspection process described focuses on CAPs, however the principles may be generally applicable.

7.1 *Conduct of inspections*

The competent authority, for inspection of the MAH's pharmacovigilance system will be the competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located. Where an additional facility in another Member State requires inspection (e.g. a database) the inspection will be carried out by the competent authority of the Member State in whose territory the facility is located.

In general, companies have a pharmacovigilance centre in the Community covering multiple products that are on the market, in the Community. These centres may also be the global pharmacovigilance centres, or the latter may be located in third countries. Where the global centres, databases, etc are located in third countries the same competent authority, as above, will be responsible for purposes of inspection on behalf of the community, if such an inspection is considered necessary. Where relevant or on request, and in particular for product specific issues, they may be assisted, or the inspection may be conducted, by an inspector and/or expert from the Rapporteur/Co-Rapporteur agency (for CAPs) or the Reference Member State agency (for MRPs/Decentralised Procedures).

7.2 *Routine inspection*

Routine inspections are carried out by the competent authority(ies) referred to in section 7.1. In general, it is anticipated that national inspection programmes will fulfill the need for routine inspections. They may be carried out on a repeated basis (see 7.4). The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory

obligations for CAPs. These inspections may be requested with one or more specific products selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the MAH and their compliance with their regulatory obligations.

In cases where a competent authority has carried out, or intends, within the required timeframe, to carry out, an inspection covering the scope of that requested, this inspection will suffice and its results will be made available to the CXMP or applicable reviewing agency.

Such inspections may be specifically requested by the CXMP.

7.3 Targeted inspections

Targeted inspections may arise when one or more of the following arise:

- Triggers for the inspection are identified which do not relate to specific concerns about a product safety or actual non-compliance e.g.:
 - The MAH has not previously been inspected.
 - The MAH has placed their first product (or only a few) on the market in the EEA.
 - The MAH has recently been or are involved in a merger or takeover process.
 - The MAH has changed their system significantly – new database system, contracting out of reporting activities etc.
- Triggers for the inspection are identified which relate to specific concerns about a product's safety or actual non-compliance e.g. significant issues relating to:
 - Specific Obligations relating to the monitoring of product safety, identified at the time of the marketing authorisation.
 - Follow-Up Measures relating to the monitoring of product safety, identified at the time of the marketing authorisation.
 - Delays in expedited or periodic reporting.
 - Incomplete reporting.
 - Submission of poor quality or incomplete PSURs
 - Inconsistencies between reports and/or other information sources.
 - Change in risk-benefit balance.
 - Failure to communicate change in risk-benefit balance.
 - Previous inspection experience.
 - Information received from other authorities.
 - Poor follow-up to requests for information from the competent authorities.
 - Product withdrawal with little or no advance notice to the EEA competent authorities.

The above are examples and other issues may trigger a targeted pharmacovigilance inspection.

7.4 *Timing of inspections*

7.4.1 Routine:

Where the pharmacovigilance system of a MAH has not been inspected previously, the CHMP or CVMP will request the relevant competent authority to carry out and report on an inspection of the system within 4 years of the placing on the market of the first CAP by that MAH. Where the system has previously been inspected, re-inspection will take place at intervals. The timing of the first inspection and any further inspection will be determined on the basis of risk analysis criteria.

The CHMP or CVMP in conjunction with the competent authority referred to in section 7.1 and the applicable pharmacovigilance and inspectors' working parties, will determine a programme for inspection in relation to CAPs. These inspections will be prioritised based on the potential risk to public or animal health, the nature of the products, extent of use, number of products that the MAH has on the EEA market, etc and risk factors such as those identified under section 7.3 (Targeted Inspections). This programme will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programme dependent on its scope. The competent authorities of the Member States are responsible for determining their national inspection programmes.

7.4.2 Targeted:

As and when the trigger is recognised and the CXMP and/or the competent authority determines that inspection is the appropriate course of action.

7.5 *Pharmacovigilance system inspections*

These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations. They may use products as examples to test the system. They may be routine or targeted.

7.6 *Product specific inspections*

These inspections focus specifically on a given product and are usually targeted as a result of triggers that have been identified – see 7.3.

7.7 *Requesting and reporting of inspections*

Inspection requests are prepared by the EMEA inspection sector in conjunction with the Rapporteur / Co-Rapporteur and the relevant competent authority. They are presented to the CXMP for adoption and once adopted are carried out by the competent authority referred to in section 7.1, on behalf of the agency. The Statement of Principles governing the partnership between the national competent authorities and the EMEA applies (an annex with respect to Pharmacovigilance inspection will be prepared).

7.8 *Inspections of contractors, licensing partners*

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with the MAH may be inspected, in order to confirm their capability to support the MAHs compliance with pharmacovigilance obligations.

7.9 *Inspections in EEA*

These may be routine or targeted.

7.10 Inspections in third countries

These may be routine or targeted. They will be included in routine inspections when considered appropriate, particularly where the main pharmacovigilance centre and databases, etc are located outside the community, for the MAH and CAP(s) in question. They will be included in targeted inspections whenever this is considered appropriate by the CXMP requesting the inspection.

7.11 Fees for inspections requested by the CHMP or CVMP

An inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the Council Regulation (EC) No 297/95 on fees, as amended and implementing rules applicable at the time.

7.12 Procedures for Pharmacovigilance inspection coordination for CAPs

The Agency will establish procedures for the administration and review of inspection requests and reports in conjunction with the CXMPs and relevant Pharmacovigilance and Inspectors working parties.

These procedures will be adopted and published in line with the policies and procedures of the Agency on such documents.

7.13 Procedures for Pharmacovigilance inspection

The established procedure for pharmacovigilance inspection prepared by the GCP Inspection Services Group will be updated as needed to include both Human and Veterinary medicinal products and to reflect the new legislative requirements where needed.

These procedures will be adopted and published in line with the policies and procedures of the Agency on such documents.

7.14 Unannounced inspection

Where particular circumstances apply it may be necessary to conduct such inspections unannounced.

7.15 Inspection reports

Each inspection will result in an inspection report, prepared in accordance with an agreed format. The inspection report will be made available to the CXMP. The inspection report will be made available to the MAH.

7.16 Follow-up of inspection findings

Where an inspection reveals non-compliances the MAH will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence. The MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

7.17 Sharing of inspection information

The competent authorities, in cooperation with the Agency and the Commission, will establish procedures for the sharing of information on inspections and their outcomes, in particular through the Pharmacovigilance Working Parties and the Inspection Services Groups.

8. REGULATORY ACTION

Under EU legislation, to protect public or animal health, competent authorities are obliged to implement pharmaceutical 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 or animal health impact of non-compliance but any instance of non-compliance may be referred for enforcement action. Action may be taken by the EMEA, the Commission or the competent authorities of the Member States as appropriate in the context. Reference should also be made to legislation at EU and national level on penalties and sanctions and implementing procedures relating to these.

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.

- *Urgent Safety Restriction*
- *Variation of the Marketing Authorisation*
- *Suspension of the Marketing Authorisation*
- *Revocation of the Marketing Authorisation*

9. PROPOSED TIMETABLE¹

This guideline will come into force in line with the revised Volume 9 of The Rules Governing Medicinal Products In The European Union.

10. REFERENCES

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*Official Journal L 136, 30/4/2004 p. 1 - 33*).

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (*Official Journal L 311, 28/11/2001 p. 67 - 128*). As amended.

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (*Official Journal L 311, 28/11/2001 p. 1 - 66*). As amended.

The Rules Governing Medicinal Products in the European Union, EudraLex Volume 9 - Pharmacovigilance Medicinal Products for Human and Veterinary use.

Council Regulation (EC) No 297/95, of 10 February 1995, on fees payable to the European Agency for the Evaluation of Medicinal Products (*Official Journal L 35, 15/2/1995 p. 1 - 5 CONSLEG - 95R0297 - 19/12/1998 - 15 p.*). As Amended.

Guideline on risk management systems for medicinal products for human use (*EMEA/CHMP/96268/2005*).