DECISION

No. 14/15.06.2007

on approval of Guideline on Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order no. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 15.06.2007, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

DECISION

Single article. – The Guideline on Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the Requirements for pharmacovigilance systems, monitoring of compliance and pharmacovigilance inspections

CHAPTER I
Scope

Art. 1. – This Guideline is a translation into Romanian and an adaptation of section „Recommendations for Marketing Authorisation Holders" – Part I – of Eudralex, Volume 9a - PHARMACOVIGILANCE – Requirements for pharmacovigilance systems, monitoring of compliance and pharmacovigilance inspections.

CHAPTER II
Introduction

Art. 2. – (1) The rapid and effective identification and assessment of medicinal product safety issues is dependent on early access to complete information: this is fundamental to Competent Authorities' (CA) and Marketing Authorisation Holders' (MAH) ability to protect public health in taking appropriate action swiftly.

(2) Marketing Authorisation Holders and Competent Authorities (CAs) have an obligation to implement medicines legislation and non-compliance with pharmacovigilance (PV) regulatory obligations could have a potentially serious health impact.

(3) This Chapter sets out the framework for implementation, in the context of the revised pharmaceutical legislation, of the monitoring of compliance with pharmacovigilance obligations and of pharmacovigilance inspections; in the same context it sets out the information to be supplied in the application giving a detailed description of the pharmacovigilance system of the Marketing Authorisation Holder and proof that the Marketing Authorisation Holder has the services of a Qualified Person responsible for Pharmacovigilance (QPPV) and the necessary means for the notification of adverse reactions (AR).

(4) This guideline is applicable for any medicinal product, whatever the marketing authorisation (MA) procedure used.

(5) Although the inspection process described focuses on centrally authorised medicinal products, however the principles are generally applicable.

(6) This Guideline does not refer to the risk management system, which includes product-specific pharmacovigilance activities described in Chapter III of the Guideline relating to the procedure which must be followed by the Marketing

Authorisation Holders during the conduct of the pharmacovigilance activities, approved through the Scientific Council Decision No. 13/2007.

2.1. Roles of the Marketing Authorisation Holder

Art. 3. – The Marketing Authorisation Holders should ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility for their medicinal products on the market and to ensure that appropriate action can be taken, when necessary. This includes the Marketing Authorisation Holder having at its disposal permanently and continuously an appropriately qualified person responsible for

pharmacovigilance residing within the European Economic Area (EEA), and the establishment of a system of pharmacovigilance.

2.2. Roles of the European Medicines Agency (EMEA)

Art. 4. – (1) The roles of the EMEA are set out in Regulation No. 726/2004/EC and further described in this Volume 9A "Notice to Applicants".

(2) Regarding the monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections, the following Articles of Regulation No. 726/2004/EC are of particular relevance:

a) Article 57(1)(c) of Regulation (EC) No. 726/2004 stating "coordination (by the EMEA) of the supervision, under practical conditions of use, of medicinal products which have been authorised 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 implementations";

b) Article 57(1)(i) of Regulation (EC) No. 726/2004 stating "coordinating the verification of compliance (by the EMEA) with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations".

2.3. Roles of the Competent Authorities in Member States

Art. 5. – (1) The roles of the Competent Authorities in Member States are set out in the updated Directive 2001/83/EC, transposed in Romanian through Law 95/2006, Title XVII- The medicinal product, in Regulation (EC) No. 726/2004 and further described in Volume 9A Notice to Applicants.

2.4. Pharmacovigilance Inspections

Art. 6. – (1) The legal basis for the conduct of Pharmacovigilance inspections is set out in Article 823 of Law 95/2006, title XVII – The medicinal product and in Article 19(1) of Regulation (EC) 726/2004.

2.5. Detailed Description of the Pharmacovigilance System to Be Included in the Marketing Authorisation Application

Art. 7. – (1) In compliance with provision of Art. 702 (4) k) of Law 95/2006, Title XVII – The medicinal product, the applicant is required to provide a detailed description of the system of pharmacovigilance and, where appropriate, of the risk management system which the Applicant will introduce.

(2) This Chapter addresses the detailed description of the pharmacovigilance system that should be supplied with the application dossier and supporting documentation that the Applicant should maintain and supply to the NMA on request.

(3) The description of the risk management system, which includes the product-specific pharmacovigilance activity, is addressed in Chapter III of the Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through Scientific Council Decision No. 13/2007.

2.6. Proof of the Services of a QPPV and of the Necessary Means to Notify Adverse Reactions, to be Included in the Marketing Authorisation Application

Art. 8. – The Applicant is required to provide proof that they have the services of a QPPV and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country, according to Art. 702 (4) q) of Law 95/2006, Title XVII – The medicinal product.

CHAPTER III
Detailed Description of the Pharmacovigilance System

III.1. Location in the Marketing Authorisation Application and Update of the Detailed Description of the Pharmacovigilance System

Art. 9. – (1) The detailed description of the pharmacovigilance system, including the proof of the availability of the services of the QPPV and the proof that the Marketing Authorisation Holder has the necessary means for the collection and notification of any adverse reaction, should be provided in Module 1, section 1.8.1 of the application dossier.

(2) The detailed description should comprise an overview of the pharmacovigilance system providing information on the key elements of that system; where aspects of the system such as the organisational arrangements are particular to the product rather than the main system of the Marketing Authorisation Holder/company (Marketing Authorisation Holder or a group of Marketing Authorisation Holders sharing the same pharmacovigilance system) this should be indicated in a product-specific addendum.

(3) The detailed description should be supported by documentation maintained by the company.

(4) Updates to the information provided in the detailed description of the pharmacovigilance system should be made as type II variations.

III.2. Statement of the Marketing Authorisation Holder Regarding the QPPV and the Means for the Notification of Adverse Reactions

Art. 10. – (1) The Applicant should provide a signed statement from the Marketing Authorisation Holder and the QPPV to mentioning that the company has their services available as QPPV and has the necessary means for the collection and notification of any adverse reaction occurring either in the Community or in a third country.

(2) This statement may make reference to the detailed description of the pharmacovigilance system (see Chapter III, Section 3 of this Guideline), indicate what is already in place, and confirm which items will be put in place before the medicinal product is placed on the market in the Community.

III. 3. Elements of the Detailed Description of the Pharmacovigilance System

Art. 11. – (1) All Marketing Authorisation Holders are required to have an appropriate system of pharmacovigilance in place.

(2) 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:

a) Information about QPPV:

- The name of the QPPV, located in the EEA. The business address and contact details should be provided in the Marketing Authorisation Application form. Companies

might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability;

- A summary Curriculum Vitae of the QPPV with the key information relevant to their role (main qualifications, training and experience);

- A summary of the job description of the QPPV.

- A description of the back-up procedure to apply in the absence of the QPPV.

b) Organisation:

- Data concerning identification and location of the company units or other organisations where the EEA and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where Individual Case Safety Reports (ICSRs) are collated and reported and where PSURs (Periodic Safety Update Reports) are prepared and processed for reporting to the Competent Authorities) and where identification of affiliates may be made in a general sense, rather than affiliate-by-affiliate.

- Identification of the point(s) in the Community at which pharmacovigilance data are accessible (to include access to ICSRs, PSURs and the global pharmacovigilance data).

- High-level organisation chart(s) providing an overview of the global and EEA pharmacovigilance units and organisations (mentioned above) and, illustrating the relationships between them, with affiliate/parent companies and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the EEA QPPV within the organisation. Individual names of people should not be included. Licensing partnerships are usually product-specific and should be indicated in a product-specific addendum in the application for that medicinal product, unless a partnership is a consistent feature of the company's organisation across most products.

- A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.

- Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the Competent Authorities. These should be limited to the major processes identified in Volume 9A Notice to Applicants.

c) Documented procedures:

An essential element of any pharmacovigilance system is that there are clear, writte procedures in place.

The following list indicates topics that should usually be covered by these written procedures. The detailed description should indicate for which of these topics there are written procedures in place, but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and in the various processes reflected in the relevant procedures.

- The activities of the QPPV and the back-up procedure to apply in their absence;

- The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of ICSRs.

- Reports of different types;

- Organised data collection schemes (solicited), unsolicited, clinical trials, literature.

- The process should ensure that reports from different sources are captured:

- EEA and third countries, healthcare professionals, sales and marketing personnel, other Marketing Authorisation Holder personnel, partners, Competent Authorities, compassionate use, patients, others;

- The follow-up of reports concerning the missing information and information concerning the evolution and outcome of the case(s);

- Detection of duplicate reports;

- Expedited reporting;

- Electronic reporting;

- PSUR:

- The preparation, processing, quality control, review (including medical review) and reporting;

- Global pharmacovigilance activities applying to all medicinal products: continuous monitoring of the safety profile of authorised medicinal products (product-specific risk management systems and pharmacovigilance planning are covered in Chapter III of Guideline on procedura care trebuie urmată de deţinătorii autorizaţiei de punere pe piaţă în desfăşurarea activităţilor de farmacovigilenţă approved through the Scientific Council Decision No. 13/2007):

- Signal detection and review;

- Risk-benefit assessment;

- Reporting and communication notifying the NMA and Healthcare Professionals of changes to the risk-benefit balance of medicinal products, etc;

- Interaction between safety issues and product defects;

- Responses to requests for information from Competent Authorities;

- Handling of urgent safety restrictions and safety variations;

- Meeting commitments to the NMA in relation to a marketing authorisation;

- Global pharmacovigilance activities applying to all medicinal products (signal detection, evaluation, reporting, communication etc.). (Product-specific risk management systems and pharmacovigilance planning are covered in Chapter III of the Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through the Scientific council Decision No. 13/2007);

- Management and use of databases and other recording systems;

- Internal audit of the pharmacovigilance system;

- Training;

- Archiving.

The detailed description of the pharmacovigilance should indicate the processes for which written procedures are available. A list and copies of the global and EEA procedures should be available within two working days on request by the NMA. Any additional local procedures should be available to respond to specific requests.

d) Databases:

A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety reports, expedited/electronic reporting, signal detection, sharing and accessing global safety information) and brief functional descriptions of these should be provided including a statement regarding the validation status of the database systems.

A statement should be included regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in Part III of Volume 9a of Eudralex.

A copy of the registration, of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to the Competent Authorities.

There should be an indication of the responsibility for the operation of the databases and their location (with reference to the location identified under Chapter IV of this Guideline).

e) Contractual Arrangements with Other Persons or Organisations Involved in the Fulfilment of Pharmacovigilance Obligations

Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main organisations to which it has subcontracted these (in particular where the role of the QPPV, the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted).

A brief description of the nature of the agreements the company established with co-marketing partners and contractors for pharmacovigilance activities should be provided.

Co-licensing or co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties made clear.

Since co-licensing or co-marketing arrangements are mainly product-specific any information on these may be provided in a product-specific addendum, in the applicable Marketing Authorisation Application. Likewise if subcontracting is product-specific this should be indicated in a product-specific addendum.

f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities. Training should include not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. Provide a brief description of the training system and indicate where the training records, Curricula Vitae (CVs) and job descriptions are filed.

g) Documentation

A brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements shall be provided. Reference can be made to the organisation charts provided under Chapter IV of this Guideline.

h) 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, quality control and review, and for ensuring corrective and preventive action.

A brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system, including auditing of sub-contractors, should be provided.

i) Supporting documentation

The Marketing Authorisation Holder should ensure that the pharmacovigilance system is in place and documented.

One of the essential features of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system.

Documentation supporting the pharmacovigilance system (and its detailed description) may be required during the pre-authorisation or post-authorisation period, for purposes such as assessment or inspection.

CHAPTER IV
Monitoring of Compliance by the NMA

Art. 12. – (1) EEA Competent Authorities have been working for many years to facilitate Marketing Authorisation Holders in meeting pharmacovigilance regulatory obligations. compliance monitoring raises concerns these should be highlighted to other Competent Authorities and in the case of centrally authorised products to the Agency, the Rapporteur/Co-Rapporteur, the Committee for Human Medicinal Products (CHMP) and the Pharmacovigilance Working Party as applicable. Deficiencies identified during compliance monitoring may lead to an inspection request.

(2) Competent Authorities should monitor Marketing Authorisation Holders for compliance with pharmacovigilance regulatory obligations.

(3) In cases of non-compliance, the Competent Authorities exchange information and will take appropriate regulatory action as required.

(4) It should be noted that enforcement action is within the competency of each Member State.

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

(6) Set out below is an outline of how compliance monitoring should be performed. In this context compliance monitoring relates to activities that are separate to inspection activities and are carried out separately to them or as a prelude or follow-up to inspection.

(7) If the monitorisation of compliance leads to the discovery of several problems, these should also be forwarded to other CAs and, in case of centrally authorised medicinal products, they should be communicated to the EMEA, as well as to the rapporteur/co-rapporteur, to the Committee for Human Medicinal Products (CHMP) and to the Pharmacovigilance Working Party (PhWP), as required; the deficiencies observed following the monitorisation of compliance may lead to a solicitation for inspection.

(8) The NMA will ensure that a system of pharmacovigilance is in place within Marketing Authorisation Holders through scrutiny of the detailed description of pharmacovigilance, procedures, safety reports and through pharmacovigilance inspections.

IV. 1. Qualified Person Responsible for Pharmacovigilance (QPPV)

Art. 13. - (1) Competent authorities will maintain a list of QPPVs within the EEA; this list will include business address and contact details (including out of hours contact).

(2) Where applicable this will include national contact points in the Member State concerned.

IV. 2. Availability of Pharmacovigilance Data

Art. 14. – The NMA should monitor (e.g. by assessment of the detailed description of the pharmacovigilance system and when inspections are carried out) that pharmacovigilance data are collected and accessible by the Marketing Authorisation Holder at least at one point within the Community.

IV. 3. Change in the Evaluation of the Risk-Benefit Balance of a Medicinal Product

Art. 15. – (1) One of the key responsibilities of Marketing Authorisation Holders is to immediately notify the Competent Authorities of any change in the balance of risks and benefits of their medicinal products.

(2) 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 the Competent Authorities.

IV. 4. Expedited Adverse Reaction Reporting

Art. 16. – (1) Requirements for expedited reporting of ICSRs are given in Chapter IV of the Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through the Scientific Council Decision No. 13/2007.

(2) 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.

(3) Methods available to the NMA for prospective monitoring of compliance with expedited reporting of adverse reactions could be:

a) Monitoring adverse reaction reports received from Marketing Authorisation Holders against other sources to determine complete failure to report;

b) Monitoring the time between receipt by Marketing Authorisation Holder and submission to Competent Authorities to detect late reporting;

c) Monitoring the quality of reports; submission of reports judged to be of poor quality may result in the follow-up procedures of Marketing Authorisation Holders being scrutinised;

d) Monitoring that all adverse reactions that are kept electronically comply with the "Note for Guidance on the Electronic Data Interchange (EDI) of ICSRs and Medicinal Product Reports (MPRs) in Pharmacovigilance in the Pre- and Post-Authorisation Phase in the EEA";

e) Checking of PSURs in order to detect under-reporting (e.g. of expedited reports);

f) Checking interim and final reports of post-authorisation safety studies to ensure that all qualifying serious reports have been submitted within 15 days;

g) At inspection there may be a review of a sample of reports on the Marketing Authorisation Holder database to assess the quality of data, determine whether the relevant reports have been expedited and are included on the EudraVigilance database, and to confirm that procedures are in place to follow up reports.

IV. 5. Periodic Safety Update Reports

Art. 17. – (1) PSURs are important pharmacovigilance documents; they provide an opportunity for Marketing Authorisation Holders to review the safety profile of their medicinal products and ensure that the Summary of Product Characteristics (SPC) and Package Leaflet are up to date.

(2) They also provide the NMA with a valuable source of pharmacovigilance data. For this reason, the NMA places great importance on compliance with periodic reporting; non-compliance may include:

a) 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;

b) Incorrect format of the document: Report not in accordance with Chapter VI of the Guideline on the procedure to be followed by the Marketing Authorisation

Holder when undertaking pharmacovigilance activities approved through the Scientific Council Decision No. 13/2007;

c) Omission of information required by Chapter VI of Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through the scientific Council Decision No. 13/2007, particularly in the following sections of the report: Update of the NMA or Marketing Authorisation Holder Actions taken for Safety Reasons, Changes to Reference Safety Information, Patient Exposure, Presentation of Individual Case History;

d) Poor quality reports: Poor documentation of adverse reactions 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 use of standardised medical terminology (e.g. MedDRA).

e) Company core data sheet (CCDS) or SPC: where changes have been made to the CCDS or SPC since the submission of the last PSUR, the covering letter does not highlight the differences between the CCDS and the EU SPC;

f) Previous requests from Competent Authorities not addressed: submission of a report where previous requests from the NMA have not been addressed (e.g. close monitoring of specific safety issues).

IV.6. Information Requested by Competent Authorities

Art. 18. – (1) 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 health.

(2) The NMA will ensure that all requests for information from Marketing Authorisation Holders have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue.

(3) The NMA will liaise with Marketing Authorisation Holders regarding the appropriate deadline, as required; failure of Marketing Authorisation Holders to provide the necessary information/data within the deadline may be considered as non-compliance.

IV. 7. Submission of Safety Variations

Art. 19. - (1) EU legislation and guidelines do not specify deadlines for submission of safety variation applications.

(2) As with responding to requests for information, deadlines for submission of safety variations will depend on the urgency and potential public health impact of the pharmacovigilance issue.

(3) The NMA 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.

(4) The NMA will liaise with Marketing Authorisation Holders regarding the appropriate deadline, as required; failure of Marketing Authorisation Holders to submit the variation application within the deadline may be considered as non-compliance.

IV. 8. CHMP Commitments in Respect of Centrally Authorised Medicinal Products

Art. 20. – (1) EU legislation or 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 CHMP Opinion.

(2) 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.

(3) These are:

a) Conditional marketing authorisations;

b) 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.

(4) Non-compliance may include:

a) Complete non-submission of data, including non-submission of specific obligations before the annual re-assessment;

b) Submission of data after the deadline agreed in the letter of undertaking from the company (without previous agreement from the Competent Authority);

c) Failure to implement a specific obligation;

d) Failure to implement a follow-up measure;

e) Poor quality of a report requested as a follow-up measure;

f) Poor quality of a report requested as a specific obligation;

g) Failure to implement an urgent provisional measure.

IV. 9. Post-Authorisation Safety Studies

Art. 21. – (1) 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 medicinal products to be identified; therefore, expedited reporting and submission to the NMA of interim and final study reports from such studies has an important role in protecting public health.

(2) Where appropriate, the NMA will scrutinise protocols prior to initiation of safety studies.

(3) The NMA should check that relevant adverse reaction reports from safety studies are expedited and monitor the submission of interim and final study reports.

(4) Provisions concerning the safety studies carried out during the post-authorisation period are available in Chapter VII of the Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through the Scientific Council Decision No. 13/2007.

IV. 10. Provision of Additional Data on Studies

Art. 22. – (1) As part of their pharmacovigilance system, companies are required to have processes in place to screen all studies for information on safety or lack of efficacy and to report on this when required (see also Chapters II and VIII of the Guideline on the procedure to be followed by the Marketing Authorisation Holder when undertaking pharmacovigilance activities approved through the Scientific Council Decision No. 13/2007).

(2) The NMA will monitor this by comparison of information received from different sources and in the course of inspections.

CHAPTER V
Pharmacovigilance Inspections

Art. 23. - (1) To ensure that Marketing Authorisation Holders comply with pharmacovigilance regulatory obligations and to facilitate compliance, the NMA will conduct pharmacovigilance inspections.

(2) There should be collaboration between the Competent Authorities to minimise duplication and maximise coverage.

(3) Inspections will be routine as well as targeted to Marketing Authorisation Holders suspected of being non-compliant.

(4) The results of an inspection will be routinely provided to the Marketing Authorisation Holder who will be given the opportunity to comment on the findings.

(5) The results will be used to help Marketing Authorisation Holders improve compliance and may also be used as a basis for enforcement action.

(6) The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.

(7) Although the inspection process described focuses on centrally authorised products, the principles may be generally applicable.

V.1. Conduct of Inspections

Art. 24 – (1) The Competent Authority for inspection of the Marketing Authorisation Holder's pharmacovigilance system will be the Competent Authority of the Member State in whose territory the Marketing Authorisation Holder's QPPV is located.

(2) Where an additional facility (e.g. a database) in another Member State requires inspection, the inspection will be carried out by the Competent Authority of the Member State in whose territory the facility is located.

(3) In general, companies have a pharmacovigilance centre in the Community covering multiple medicinal products that are on the market, in the Community.

(4) 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.

(5) 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 Member State (for centrally authorised medicinal products) or the Reference Member State (for mutual recognition procedures/decentralised procedures).

V.2. Routine Inspections

Art. 25. – (1) Routine inspections are carried out by the Competent Authority(ies) referred to in Chapter V, Section 1 of this Guideline.

(2) In general, it is anticipated that national inspection programmes will fulfil the need for routine inspections; they may be carried out on a repeated basis.

(3) The focus of these inspections is to determine that the Marketing Authorisation Holder has personnel, systems and operational facilities in place to meet their regulatory obligations for centrally authorised products.

(4) These inspections may be requested with one or more specific medicinal 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 Marketing Authorisation Holder and their compliance with their regulatory obligations.

(5) 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 CHMP or applicable reviewing agency.

(6) Such inspections may be specifically requested by the CHMP.

(7) Where the pharmacovigilance system of a Marketing Authorisation Holder has not been inspected previously, the CHMP 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 centrally authorised product by that Marketing Authorisation Holder.

(8) 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.

(9) The CHMP, in conjunction with the Competent Authority referred to in Chapter V, Section 1 and the applicable Pharmacovigilance and Inspectors' Working Parties, will determine a programme for inspection in relation to centrally authorised medicinal products.

(10) This inspection will be prioritised based on the potential risk to public health, the nature of the medicinal product, extent of use, number of medicinal products that the Marketing Authorisation Holder has on the EEA market, etc. and risk factors such as those identified under Chapter V, Section 3 of this Guideline.

(11) 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.

(12) The NMA is responsible for determining the national inspection programme.

V.3. Targeted Inspections

Art. 26. – (1) Targeted inspections may be conducted as and when the trigger is recognised and the CHMP and/or the NMA determines that inspection is the appropriate course of action.

(2) The necessity of targeted inspections may arise when one or more of the following arise:

a) Triggers for the inspection are identified which do not relate to specific concerns about a medicinal product's safety or actual non-compliance, e.g.:

- The Marketing Authorisation Holder has not previously been inspected;
- The Marketing Authorisation Holder has placed his/her first medicinal product on the market in the EEA;
- The Marketing Authorisation Holder has recently been or is involved in a merger or takeover process;
- The Marketing Authorisation Holder has changed their system significantly (e.g. new database, contracting out of reporting activities).

b) Triggers for the inspection are identified which relate to specific concerns about a medicinal product's safety or actual non-compliance, e.g. significant issues relating to:

- Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of medicinal 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 other information sources;
- Changes in the 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 NMA;
- Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the NMA or the EMEA as applicable;
- Product withdrawal with little or no advance notice to the EEA Competent Authorities.

(3) The above are examples but there are also other issues that may trigger a targeted pharmacovigilance inspection; the presence of a trigger will not always lead to the conduct of an inspection.

V.4. Pharmacovigilance System Inspections

Art. 27. – (1) These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations.

(2) They may use medicinal products as examples to test the system.

(3) These inspections may be routine or targeted.

V.5. Product-specific inspections

Art. 28. These information focus specifically on a given medicinal product and are usually targeted as a result of triggers that have been identified (see Chapter V, section 1 of this Guideline).

V.6. Requesting and Reporting of Inspections

Art. 29. - Inspection requests are prepared by the EMEA's inspection sector in conjunction with the Rapporteur/Co-Rapporteur and the relevant Competent Authority. They are presented to the CHMP for adoption and once adopted are carried out by the EMEA Competent Authority referred to in Chapter V, section 1 of this Guideline.

V.7. Inspections of Contractors and Licensing Partners

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

V.8. Inspections in EEA

Art. 31. - These may be routine or targeted.

V.9. Inspections in third countries

Art. 32. - These maybe 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 Marketing Authorisation Holder and centrally auhorised medicinal product(s) in question; they will be included in targeted inspections whenever this is considered appropriate by the authority requesting the inspection.

V.10. Fees for Inspections Requested by the CHMP

Art. 33. – In case of centrally authorised medicinal products, an inspection fee(s) (and inspector's 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.

V.11. Procedures for Coordination of Pharmacovigilance Inspection for Centrally authorised Medicinal Products

Art. 34. – (1) The EMEA will establish procedures for the administration and review of inspection requests and reports in conjunction with the CHMP and relevant Pharmacovigilance and Inspectors' Working Parties.

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

V.12. Procedures for Pharmacovigilance Inspections

Art. 35. – (1) Procedures for the pharmacovigilance inspection are prepared by the Good Clinical Practice Working Party, in association with representatives of the pharmacovigilance inspectors of the national Competent Authorities and representatives of the Pharmacovigilance Working Parties and will be updated when needed.

(2) These procedures will be adopted and published according to the policy and EMEA procedures concerning these documents.

V.13. Unexpected inspections

Art. 36. – It is anticipated that the majority of inspections shall be announced; however, occasionally, an inspection may be unannounced or briefly announced.

V.14. Inspection reports

Art. 37. – Each inspection finishes with an inspection report, issued in accordance with an established format; the inspection report is made available for the CHMP and MAH.

V.15. Post-inspection findings

Art. 38. – (1)When an inspection evinces the existence of noncompliances, the MAH is required to set up a plan of coercive measures relating to those findings and to avoid their reoccurence.

(2) The MAH may be asked to provide reports and evidence of the progress and fulfilment of the measure plan when necessary.

(3) Following an adequate timeframe, a re-inspection may be conducted in order to check success and progress of these coercive measures.

V.16. Sharing of inspection information

Art. 39. - The NMA and the European Commission, in co-operation with the EMEA, will establish procedures for the sharing of information on inspections and their outcomes, in particular through the Pharmacovigilance Working Party and the Inspection Services Group.

CHAPTER VI
Regulatory actions

Art. 40 – (1) Under EU legislation, to protect public health, the NMA is obliged to implement pharmaceutical legislation and to ensure compliance with pharmacovigilance obligations.

(2) 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.

(3) Action may be taken by the EMEA, the Commission or the NMA as appropriate in the context.

(4) Reference should also be made to legislation at EU and national level on penalties and sanctions and implementing procedures relating to these.

(5) In addition, in the event of non-compliance, regulatory options include the following:

a) Education and Facilitation Marketing Authorisation Holders may be informed of non-compliance and advised on how this can be remedied.

b) Inspection: Non-compliant Marketing Authorisation Holders may be inspected and then re-inspected to ensure compliance is achieved.

c) Warning: The NMA may issue a formal warning reminding Marketing Authorisation Holders of their pharmacovigilance regulatory obligations.

d) Naming non-compliant Marketing Authorisation Holders: the NMA will consider a policy of making public a list of Marketing Authorisation Holders found to be seriously or persistently non-compliant.

e) Urgent Safety Restrictions: In accordance with this Guideline and other regulations.

f) Variation of the Marketing Authorisation: In accordance with this Guideline and other regulations.

g) Suspension of the Marketing Authorisation: in accordance with the Guideline and other regulations.

h) Revocation of the Marketing Authorisation: In accordance with this Guideline and other regulations.