1 19 June 2012
2 EMA/119871/2012
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4 Guideline on good pharmacovigilance practices (GVP)

5 Module III – Pharmacovigilance inspections

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	25 May 2012
Draft agreed by ERMS FG	30 May 2012
Draft adopted by Executive Director	22 June 2012
Start of public consultation	27 June 2012
End of consultation (deadline for comments)	24 August 2012
Anticipated date for coming into effect after finalisation	Q4 2012

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III.A. Introduction

This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and outlines the role of the different parties involved. General guidance is provided under III.B., while III.C. covers the overall operation of pharmacovigilance inspections in the EU.

In order to determine that marketing authorisation holders comply with pharmacovigilance obligations established within the EU, and to facilitate compliance, competent authorities of the Member States concerned shall conduct, in cooperation with the Agency, pharmacovigilance inspections of marketing authorisation holders or any relevant third parties employed to fulfil a marketing authorisation holder's pharmacovigilance obligations. Such inspections shall be carried out by inspectors appointed by the national competent authorities and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX of Directive 2001/83/EC [DIR Art 111(1), Art 111(1)(d)]. In particular, marketing authorisation holders are required to provide, on request, a description of the pharmacovigilance system in a master file, which will be used to inform inspection conduct [DIR Art 23(4) and REG Art 16(4)] (see Module II).

The objectives of pharmacovigilance inspections are:

- to determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- to identify, record and address non-compliance which may pose a risk to public health;
- to use the inspection results as a basis for enforcement action, where considered necessary.

For marketing authorisation holders of centrally authorised products, it is the responsibility of the supervisory authority for pharmacovigilance to verify, on behalf of the EU, that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC [REG Art 19]. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located [REG Art 18(3)] either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)]. The supervisory authority may conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 18(3)].

For marketing authorisation holders of non-centrally authorised products (i.e. nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure), it is the responsibility of the competent authority of the Member State concerned, in cooperation with the Agency, to ensure by means of inspection that the legal requirements governing medicinal products are complied with. This cooperation shall consist of the sharing of information between national competent authorities and the Agency concerning inspections that are planned and those that have been conducted [DIR Art 111(1)].

Pharmacovigilance inspection programmes will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate "for cause" inspections, which have been triggered to examine suspected non-compliance or potential risks, usually with impact on a specific product(s).

There shall be cooperation between national competent authorities and the Agency to minimise duplication and maximise the use of available resources. National competent authorities and the Agency will make use of the shared information on planned and conducted inspections to facilitate this and to adapt the scope and/or timing of their inspections.

The results of an inspection will be routinely provided to the inspected entity [DIR Art 111(3) and 111(8)], who will be given the opportunity to comment on any non-compliance identified [DIR Art 111(8)]. Any non-compliance should also be rectified by the marketing authorisation holder in a timely manner through the implementation of a corrective and preventative action plan.

If the outcome of the inspection is that the marketing authorisation holder does not comply with the pharmacovigilance obligations, the Member State concerned shall inform the other Member States, the Agency and the Commission [DIR Art 111(8)].

Sharing of information and communication between inspectors and assessors from the Pharmacovigilance Risk Assessment Committee (PRAC) and from the Committee for Medicinal Products for Human Use (CHMP) or the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), is very important in relation to issues of community interest and, where considered appropriate, for the proper follow-up of inspections and the provision of recommendations on actions to be taken.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties [DIR Art 111(8)]. Regulation (EC) No 658/2007 also empowers the Commission to impose financial penalties on marketing authorisations holders to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

Information on the conduct and outcome of pharmacovigilance inspections and the follow-up and evaluation of the consequences may be made publicly available as part of the overall transparency of pharmacovigilance activities.

III.B. Structures and processes

III.B.1. Inspection types

III.B.1.1. System and product-related inspections

Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

III.B.1.2. Routine and "for cause" pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

For cause pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. For cause inspections may arise when, for example, one or more of the triggers listed below are identified:

- risk-benefit balance of the product:
  - change in the risk-benefit balance where further examination through an inspection is considered appropriate;
  - delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
  - communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the national competent authorities or Agency, as applicable;
  - non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the national competent authorities and/or the Agency;
  - suspension or product withdrawal with little or no advance notice to the competent authorities;
- reporting obligations (expedited and periodic):
  - delays or omissions in reporting;
  - poor quality or incomplete reports;
  - inconsistencies between reports and other information sources;
- requests from competent authorities:
  - failure to provide the requested information or data within the deadline specified by the competent authorities;
  - poor quality or inadequate provision of data to fulfil requests for information from the competent authorities;
- fulfilment of commitments:
  - concerns about the status or fulfilment of risk management plan (RMP) commitments;
  - delays or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation;
  - poor quality of reports requested as follow-up measures or specific obligations;
- inspections:

- delays in the implementation or inappropriate implementation of corrective and preventative actions;
- information such as non-compliance or product safety issues from other types of GXP inspections ;
- inspection information received from other authorities (EU or non-EU), which may highlight issues of non-compliance;

- others:
  - concerns following review of the pharmacovigilance system master file;
  - non-inspection related information received from other authorities, which may highlight issues of non-compliance;
  - other sources of information or complaints.

III.B.1.3. Pre-authorisation inspections

Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorisation application [REG Art 19]. Pre-authorisation inspections are not mandatory, but may be requested in specific circumstances. Principles and procedures for requesting pre-authorisation inspections should be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorisation. The following aspects shall be considered during the validation phase and/or early during the assessment phase:

- the applicant has not previously operated a pharmacovigilance system within the EU or is in the process of establishing a new pharmacovigilance system;
- previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance. If the marketing authorisation holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorisation pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorisation is granted;
- due to product-specific safety concerns, it may be considered appropriate to examine the applicant's ability:
  - to implement product specific risk-minimisation activities; or
  - to meet specific safety conditions which may be imposed; or
  - to manage routine pharmacovigilance for the product of concern (e.g. anticipated significant increase in adverse reaction reports when compared to previous products).

In most cases, a risk assessment based on a combination of product-specific and system-related issues should be performed before a pre-authorisation pharmacovigilance inspection is requested.

If the outcome of the pre-authorisation inspection raises concerns about the applicant's ability to comply with the requirements laid down in the Regulation and the Directive, the following recommendations may be considered:

- non approval of the marketing authorisation;

- a re-inspection prior to approval of the marketing authorisation to confirm that critical findings and recommendations have been addressed;
- granting of the marketing authorisation with the recommendation to perform an early post-authorisation pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the EU routine programme of pharmacovigilance inspections (see III.B.2.);
- imposition of safety conditions to the marketing authorisation based on Article 21a of Directive 2001/83/EC.

III.B.1.4. Post-authorisation inspections

Post-authorisation pharmacovigilance inspections are inspections performed after a marketing authorisation is granted and are intended to examine whether the marketing authorisation holder complies with its pharmacovigilance obligations. They can be any of the types mentioned under III.B.1.1 and IIIB.1.2.

III.B.1.5. Announced and unannounced inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

III.B.1.6. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventative actions in response to an earlier inspection.

III.B.1.7. Remote inspections

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorisation holder, or third party to the marketing authorisation holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the EU or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has

revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

III.B.2. Inspection planning

Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programmes. Sharing of information and communication between inspectors and assessors is important to ensure successful prioritisation and targeting of these inspections.

Factors which may be taken into consideration, as appropriate, by the competent authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:

- inspection related:
  - compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP);
  - re-inspection date recommended by the inspectors or assessors as a result of a previous inspection;
- product related:
  - product with additional pharmacovigilance activities or risk-minimisation activities;
  - authorisation with conditions associated with safety, e.g. requirement for post-authorisation safety studies (PASS) or designation for additional monitoring;
  - product(s) with large sales volume, i.e. products associated with large patient exposure in the EU;
  - product(s) with limited alternative in the market place;
- applicant and marketing authorisation holder related:
  - marketing authorisation holder that has never been subject to a pharmacovigilance inspection;
  - marketing authorisation holder with many products on the market in the EU;
  - resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake;
  - applicant with no previous marketing authorisations in EU (centrally authorised products;
  - negative information and/or safety concerns raised by competent authorities, other bodies outside the EU or other GXP areas;
  - changes in the marketing authorisation holder organisation, such as mergers and acquisitions;
- pharmacovigilance system related:
  - marketing authorisation holder with sub-contracted pharmacovigilance activities (qualified person responsible for pharmacovigilance in the EU (QPPV) function, reporting of safety data etc.) and/or multiple contracting partners;

- change of QPPV or person responsible for pharmacovigilance at a national level since the last inspection;
- changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as, information about transferred or migrated data;
- changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted
- delegation or transfer of pharmacovigilance system master file management.

National competent authorities and the Agency may solicit information from marketing authorisation holders for risk-based inspection planning purposes if it is not readily available elsewhere.

III.B.3. Sites to be inspected

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. The pharmacovigilance system master file should describe the system such that it is quite clear where the main pharmacovigilance activities are performed.

The sites to be inspected may be located in the EU (e.g. EU QPPV site) or outside the EU. Inspections of sites outside the EU might be appropriate where the main pharmacovigilance centre, databases and/or activities are located outside the EU and it would be otherwise inefficient or impossible to confirm compliance from a site within the EU. Member States and the Agency shall cooperate in the coordination of inspections in third countries [DIR Art 111(1)].

The type and number of sites to be inspected should be selected appropriately to ensure that the key objectives within the scope of the inspection are met.

III.B.4. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by competent authorities of Member States and whether it is a system or product-related inspection (a description of the types of inspection, inspection triggers and points to consider for the different types of inspection is provided in III.B.1.).

The following elements should be considered when preparing the scope of the inspection, as applicable:

- information supplied in the pharmacovigilance system master file;
- information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency such as EudraVigilance reporting and data quality audits;
- specific triggers (see III.B.1.2. for examples of triggers);

It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

III.B.4.1 Routine pharmacovigilance inspections

Routine pharmacovigilance inspections conducted on behalf of the EU, should examine compliance with EU legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:

- individual case safety reports (ICSRs):
  - collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including third parties and departments other than drug safety;
  - assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of ICSRs from within the EU, examples of ICSRs reported from outside the EU should be examined as part of this review (if applicable);
  - follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
  - reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
  - record keeping for ICSRs;
- periodic safety update reports (PSURs), (as applicable):
  - completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
  - addressing safety topics, providing relevant analyses and actions;
  - formatting according to requirements;
  - timeliness of submissions;
- ongoing safety evaluation;
  - use of all relevant sources of information for signal detection;
  - appropriately applied methodology concerning analysis;
  - appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
  - implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
  - timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
  - implementation of approved changes to safety communications and product information, including internal distribution and external publication;
- interventional and non-interventional clinical trials:
  - reporting suspected unexpected serious adverse reactions (SUSARs) according to Directive 2001/20/EC and non-interventional study cases according to Directive 2001/83/EC;
  - receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);

- submission of study results and relevant safety information (e.g. annual safety reports, development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
- appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
- the inclusion of study data in ongoing safety evaluation;

- pharmacovigilance system:
  - QPPV roles and responsibilities, e.g. access to quality system, pharmacovigilance system master file, performance metrics, audit and inspection reports, their ability to take action to improve compliance;
  - the roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
  - accuracy, completeness and maintenance of the pharmacovigilance system master file;
  - quality and adequacy of training, qualifications and experience of staff;
  - coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
  - fitness for purpose of computerised systems;
  - contract and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.

The inspection may include the system for the fulfilment of conditions of a marketing authorisation and the implementation of risk–minimisation activities, as they relate to any of the above safety topics.

III.B.4.2 For cause inspections

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed in III.B.4.1 and below, may be relevant:

- QPPV involvement and awareness of product-specific issues;
- in-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

III.B.4.3 Re-inspections

For the scope of a re-inspection, the following aspects should be considered:

- review of the status of the system and/or corrective and preventative action plan(s) resulting from previous pharmacovigilance inspection(s);
- review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in QPPV);
- review of process and/or product-specific issues identified from the assessment of information provided by the marketing authorisation holder, or not covered in a prior inspection.

The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example if a long time has elapsed since the previous inspection, in which case the elements listed in III.B.4.1. may be considered for the inspection scope, as appropriate.

III.B.5. Inspection process

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed community pharmacovigilance inspection procedures developed by the PhVIWG to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU. These community procedures will be published as annexes to this Module. Improvement and harmonisation of inspection conduct will be promoted by agreed processes and procedures, joint inspection(s) and sharing of experience and training by national competent authority inspectorates.

The community procedures on pharmacovigilance inspections will cover, at least, the following processes:

- sharing of information;
- inspection planning;
- pre-authorisation inspections;
- coordination of pharmacovigilance inspections in the EU;
- coordination of third country inspections and inspection of contractors;
- preparation of pharmacovigilance inspections;
- conduct of pharmacovigilance inspections;
- reporting of pharmacovigilance inspections and inspection follow-up;
- communication and prioritisation of pharmacovigilance inspections and findings;
- Interaction with PRAC in relation to isnpections and its follow up;
- record-keeping and archiving of documents obtained or resulting from the pharmacovigilance inspections;
- unannounced inspections;
- sanctions and enforcement in case of serious non-compliance;
- recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

These procedures will be revised and updated as deemed necessary. New procedures may also be developed when the need is identified in relation to the inspection process.

III.B.6. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventative action plan is completed. The following follow-up actions should be considered, as appropriate:

- review of the marketing authorisation holder's corrective and preventative action plan;

- review of the periodic progress reports, when deemed necessary;
- re-inspection to assess appropriate implementation of the corrective and preventative action plan;
- requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;
- requests for issuing safety communications, including amendments of marketing and/or advertising information;
- requests for a meeting with the marketing authorisation holder to discuss the deficiencies, the impact of the deficiencies and action plans;
- communication of the inspection findings to other regulatory authorities (including outside the EU);
- other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorisations or clinical trial authorisations).

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections. Recommendations on follow-up actions will be provided in the pharmacovigilance inspection reports and others may arise from the interaction between inspectors and assessors in line with the EU pharmacovigilance inspection procedure on inspection follow-up, which will be included in the compilation of community procedures on pharmacovigilance inspections mentioned in III.B.5.

III.B.7. Regulatory actions and sanctions

Under EU legislation, in order to protect public health, competent authorities are obliged to implement the EU pharmaceutical legislation and to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance 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 the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. Action may be taken by the Agency, the Commission or the competent authorities of the Member States as appropriate. As stated in Article 111(8) of Directive 2001/83/EC, where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties. Moreover Regulation (EC) No 658/2007 also empowers the Commission, at the request of the Agency, to impose financial penalties on the holders of marketing authorisations to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- education and facilitation: national competent authorities may communicate with marketing authorisation holder representatives (e.g. in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorisation holder's proposals for corrective and preventative actions;
- provision of information to other competent authorities, the Agency or third country regulators under the framework of confidentiality arrangements;

- inspection: non-compliant marketing authorisation holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which competent authorities may issue stating the legislation and guideline that has been breached, reminding marketing authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- competent authorities may consider making public a list of marketing authorisation holders found to be seriously or persistently non-compliant;
- actions against a marketing authorisation(s) or authorisation application(s) e.g.
  - Urgent Safety Restriction;
  - variation of the marketing authorisation;
  - suspension or revocation of the marketing authorisation;
  - delays in approvals of new marketing authorisation applications until corrective and preventative actions have been implemented or the addition of safety conditions to new authorisations;
  - requests for pre-authorisation inspections;
- product recalls e.g. where important safety warnings have been omitted from product information;
- action relating to marketing or advertising information;
- amendments or suspension of clinical trials due to product-specific safety issues;
- administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

III.B.8. Record management and archiving

The principles and requirements to be followed will be described in the community procedure on Record Keeping and Archiving of Documents Obtained or Resulting from the Pharmacovigilance Inspections referred to in III.B.5.

III.B.9. Qualification and training of inspectors

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by their Member States or by the CHMP should be officials of, or appointed by, the Member State in accordance with national regulation and follow the provisions of the national competent authority.

It is recommended that inspectors are appointed based upon their experience and the minimum requirements defined by the national competent authority.

The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections. They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes should be in place in order to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of the concerned competent authority.

III.B.10. Quality management of pharmacovigilance inspection process

Quality of the pharmacovigilance inspection process is managed by the national competent authorities and covered by their pharmacovigilance systems and associated quality systems, meaning that the process is also subject to audit. Guidance on establishment and maintenance of a quality assured pharmacovigilance system is provided in Module I.

Quality and consistency of the inspections is facilitated by the community procedures for pharmacovigilance inspections developed by the PhVIWG to support the mutual recognition of inspections within the EU mentioned in III.B.5.

III.C. Operation of the EU network

III.C.1. Sharing of information

The Agency and the Member States shall cooperate to facilitate the exchange of information on inspections and in particular:

- Information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities in the EU and optimise the inspection resources.
- Information on the scope of the inspection in order to focus future inspections.
- Information on the outcome of the inspection, in particular when the outcome is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with the requirements laid down in legislation and relevant guidance. A summary of the critical and significant major findings and a summary of the corresponding corrective and preventative actions with their follow-up(s) should be exchanged.

Tools and procedures will be developed at EU level to facilitate and optimise the exchange and sharing of information and the communication across the Union.

III.C.2. Role of the European Medicines Agency

III.C.2.1. General Role of the Agency

Regarding the monitoring of compliance with regulatory pharmacovigilance obligations and pharmacovigilance inspections, the roles of the Agency are set out in Article 57(1)(c) and Article 57(1)(i) of Regulation (EC) No 726/2004 and can be summarised as follows:

- Coordination of the monitoring of medicinal products for human use which have been authorised within the Union, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;
- Coordination of the verification of compliance with pharmacovigilance obligations.

Pharmacovigilance inspections coordinated by the Agency are performed by the supervisory authority concerned as outlined in III.C.3.2. The supervisory authority may be assisted by other national competent authorities, when required.

As part of this coordination role the Agency is responsible for:

- establishing and maintaining processes through the PhVIWG to support the consistency and quality of pharmacovigilance inspections of marketing authorisation holders with centrally authorised products conducted by inspectorates of the national competent authorities;
- coordinating and ensuring the implementation of a risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products (see III.B.2) enabling the timely sharing of information on planned and conducted pharmacovigilance inspections between Member States, with the aim of reducing duplication of inspection activity and facilitating mutual recognition of inspection findings;
- coordinating “for cause” inspections, as requested by the CHMP. If a “for cause” inspection has been or will be conducted in a similar timeframe as a routine one, it may replace the need for the planned routine inspection and the programme shall be revised to reflect this;
- coordinating third country inspections: according to Article 111(1) of the Directive 2001/83/EC, the Agency shall cooperate in the coordination of inspections in third countries. Member States should liaise with the Agency when the need for an inspection of a third country site is identified in order to ensure productive use of pharmacovigilance inspection resource in the interests of the Union;
- communication and follow-up of inspections of community interest across the Agency, the PRAC, the CHMP, the CMD(h), the European network and with third country regulators, whenever confidentiality arrangements are in place to facilitate this.

III.C.2.2. Role of the PRAC

The PRAC may make recommendations on the need and scope of "for cause" pharmacovigilance inspections related to medicinal products of community interest.

The PRAC may, in relation to issues of community interest and where considered appropriate, review the outcome of pharmacovigilance inspections and assess marketing authorisation holder-related corrective and preventative action plan submission(s) in order to make or endorse further recommendations on actions to be taken and their follow-up.

The PRAC is also responsible for providing input in the preparation of and agreeing on the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products outlined in III.B.2 and III.C.3.3.

The general role of the PRAC is detailed in the PRAC mandate and rules of procedures.

III.C.2.3. Role of the CHMP

The CHMP is responsible for the request of pharmacovigilance inspections in the context of the centralised procedure and for the endorsement of the recommendations made by the PRAC in relation

to the outcome of these inspections and their follow-up. The CHMP is also responsible for the adoption of the risk-based programme for routine pharmacovigilance inspections outlined in III.B.2 and III.C.3.3.

III.C.2.4. Role of the CMD(h)

It is the responsibility of the CMD(h) to cooperate with the PRAC in the context of products authorised via the mutual recognition or decentralised procedures to take forward any recommendation from the PRAC in relation to the outcome of pharmacovigilance inspections and their follow-up.

III.C.3. Role of the Member States

III.C.3.1 General Considerations

Member States should establish the legal and administrative framework within which pharmacovigilance inspections operate, including the definition of the rights of inspectors for inspecting pharmacovigilance sites and access to pharmacovigilance data.

Member States should provide sufficient resources and appoint adequately qualified inspectors to ensure effective determination of compliance with good pharmacovigilance practice. The inspector(s) appointed may be accompanied, when needed, by expert(s) on relevant areas. A Member State may also request assistance from another Member State, in which case, access to the inspection sites and data by the Member State providing assistance is desirable.

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed community pharmacovigilance inspection procedures developed by the PhVIWG to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU as mentioned in section III.B.5.

The scheduling and conduct of these inspections will be driven by the preparation of inspection programmes based on a systematic and risk-based approach as outlined in III.B.2 and III.C.3.3.

The national competent authorities, when preparing inspection programmes, should verify the inspection status of the marketing authorisation holders they plan to inspect by considering the information shared on planned or conducted inspections under the programmes in other Member States in order to assure coordination of inspection activities, prevent unnecessary duplication and to make the most efficient use of inspection resources.

When the pharmacovigilance system a national competent authority plans to inspect is the same as that already inspected by another national competent authority, sharing of information on the scope and outcomes of previous inspections and consideration of the national supervisory requirements, will help to define the objective, scope and timing of that national inspection.

A common repository, accessible to all Member States, the Agency and the Commission, should be created to facilitate this information sharing on pharmacovigilance inspections.

III.C.3.2 Role of the Supervisory Authority

The concept of the supervisory authority applies only in relation to centrally authorised products. According to Article 18 of Regulation (EC) 726/2004, the supervisory authority for the conduct of pharmacovigilance inspections shall be the competent authority of the Member State in which the pharmacovigilance system master file is located.

The supervisory authorities for pharmacovigilance are responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC. They may, if this is considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 19].

Where the sites selected to be inspected are located outside EU, the same supervisory authority as above will be responsible for the inspection on behalf of the Union. Where relevant or on request, and in particular for product-specific issues, the inspection may be conducted or assisted by inspector(s) from the Rapporteur or Co-Rapporteur Member State and/or expert(s) from the Rapporteur or Co-Rapporteur Member State or from other Member States as appropriate.

III.C.3.3. Inspection Programmes

A programme for routine inspections for centrally authorised products, will be determined by the Agency in conjunction with the supervisory authorities of the Member States, the PhVIWG, the PRAC and the CHMP. These inspections will be prioritised based on the potential risk to public health, considering the factors listed in III.B.5. As a general approach, a marketing authorisation holder should be inspected on the basis of risk-based considerations, but at least once every 4 years.

If the same pharmacovigilance system is used for a variety of authorisation types (centralised and national, mutual recognition and decentralised), then the results of a supervisory authority inspection may be applicable for all products covered by that system.

This routine inspection programme will be separate from any “for cause” inspections, but if a “for cause” inspection takes place it may replace the need for one under this programme, dependent on its scope.

Member States are also responsible for the planning and coordination of pharmacovigilance inspections within their territory in relation to products authorised nationally or via the mutual recognition or decentralised procedures in order to ensure compliance with the legislation within their own Member States and to verify the effectiveness of the marketing authorisation holder’s pharmacovigilance system at national level.

As indicated in III.C.3.1, based on the information from other inspections, the national competent authority will prioritise the inspections in its national programme and will use the information for the preparation of an appropriate scope for the national inspection. For example, national competent authorities may seek to verify the fulfilment of requirements concerning the national implementation of specific risk-minimisation measures, national communications concerning safety, locally conducted safety studies, or issues linked to national health care systems. A broader examination of pharmacovigilance applied to particular products of national interest may also be appropriate if this was not covered within the scope of a supervisory authority inspection.

III.C.4. Role of the Marketing Authorisation Holders and Applicants

Marketing authorisation holders with authorised products and applicants who have submitted new applications under the centralised procedure are subject to pharmacovigilance inspections (see III.B.1). Therefore both have responsibilities in relation to inspections, including but not limited to the following:

- Always to be inspection-ready as inspections may be unannounced.
- To maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the pharmacovigilance system master file as required by Article 23(4) of Directive 2001/83/EC and and Article 16(4) of Regulation (EU) 726/2004.
- To ensure that the sites selected for inspection agree to be inspected before the inspection is performed.
- To make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection.
- To ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified.
- To ensure that relevant pharmacovigilance data is accessible from at least one point in the Union [DIR Art 107(1)].
- To ensure that if critical or significant findings are observed during an inspection, appropriate and timely corrective and preventative action plans are implemented.

III.C.5. Inspection Fees

For inspections requested by the CHMP, an inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products as amended and implementing rules applicable at the time. For pharmacovigilance inspections performed in the context of national, mutual recognition and decentralised procedures similar fees may or may not apply depending on the legal requirements of the Member State carrying out the inspection.

III.C.6. Transparency

Information on the conduct and outcome of pharmacovigilance inspections and their follow-up will be made publicly available without prejudice to Regulation 1049/2001.