Compilation of Community Procedures on Inspections and Exchange of Information

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Published in Agreement with the European Commission by the European Medicines Agency
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Introduction

The Compilation of Community Procedures on Inspections and Exchange of Information, formerly known as the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections, is a tool for facilitating co-operation between the GMP inspectorates of the Member States and a means of achieving harmonisation. The procedures within it provide the basis for national procedures that form part of the national GMP inspectorates’ quality systems. These quality systems are based on a framework laid down in one of the documents of the Compilation. In July 2010 documents connected with Good Distribution Practice (GDP) inspections started to be added to the Compilation.

The contents of the Compilation of Procedures are constantly updated developed and agreed, under the co-ordination of the European Medicines Agency, by representatives of the GMP Inspectorates of each member state, including those supervising the manufacture and import of veterinary medicinal products only. Once agreed, they are adopted by the European Commission and then published on its behalf by the European Medicines Agency.

The Heads of Medicines Agencies have agreed to the setting up of a joint audit programme of GMP inspectorates to maintain mutual confidence in the GMP inspection systems of each member state by the other member states, and the Compilation provides criteria on which the audits are based.

Member states are obliged to take account of the Compilation of Procedures by virtue of Art. 3(1) of Directive 2003/94/EC. Until such time as the corresponding GMP directive for veterinary medicinal products, Directive 91/412/EEC, is amended accordingly, GMP Inspectorates dealing exclusively with veterinary medicinal products have voluntarily agreed to abide by it, although it is recognised that the formats for inspection reports, manufacturing authorisations and GMP certificates are of a binding nature by virtue of Art. 51 of Directive 2001/82/EC, as amended.
Quality Systems Framework for GMP Inspectorates

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Title | Quality Systems Framework for GMP Inspectorates
--- | ---
Date of adoption | November 2007
Date of entry into force | April 2008
Supersedes | Version in force from March 2004
Reason for revision | Following the implementation of ICH Q9 guideline the text was amended to introduce a quality risk management approach including minor editorial changes
Notes | None
Quality Systems Framework for GMP Inspectorates

1. Introduction

1.1 One of the main purposes of the GMP/GDP Inspectors Working Group is to establish and maintain a system for mutual recognition of national inspections in respect of the manufacture and, where relevant, wholesale distribution of medicinal products and for the administrative collaboration between Member States (MS) of the European Economic Area (EEA). The general requirements for national pharmaceutical inspectorates are to fulfil the requirements of national legislation and of the relevant European Directives for EEA countries. Specific obligations of inspections as contained in national law and if any European Directives must be included in the national Inspectorate’s quality systems.

1.2 This document outlines the quality system requirements for GMP pharmaceutical inspectorates. It is intended that each GMP pharmaceutical inspectorate uses the document as the basis for developing and implementing its quality system and for preparing the quality manual. In addition to providing a basis for self-assessment and a reference document for use by external assessors, establishing and maintaining an effective quality system will generate confidence within and between GMP national pharmaceutical inspectorates in the assessment of compliance with good manufacturing practice and/or good wholesale distribution practice.

1.3 National GMP pharmaceutical inspectorates, the European Commission (EC), the European Medicines Agency (EMEA) and the pharmaceutical Inspection Cooperation Scheme – (PIC/S) should co-operate with one another in exchanging experiences in the maintenance and operation of quality systems and in the further development of this document.

1.4 Only on voluntary basis, this document could be useful for (other) inspectorates assessing compliance with GXP or for the inspection of pharmacies.

1.5 In preparing this text, the working group was advised by:

EN ISO/IEC 17020:2005 General criteria for the operation of various types of bodies performing inspections;

EN ISO/IEC 17023:2006 General requirements for bodies operating assessment and certification/ registration of quality system;

ISO 9001-2000 Quality management systems-Requirements;

ISO 9004-2000 Quality management systems: guidelines for performance improvements;

ISO 19011 : 2002 Guidelines for quality and/or environmental managerial systems auditing;

PI 002-1 : 2000 Recommendations on quality system requirements for pharmaceutical inspectorates;
2. Purpose

2.1 The primary purpose of a quality system is to ensure that adequate quality standards are maintained. The purpose of adopting a common standard for quality system requirements is to achieve consistency in inspection standards between GMP national pharmaceutical inspectorates and thus to facilitate mutual recognition of those inspectorates. This standard should facilitate implementation of the European Joint Audit Programme and PIC/S Joint Re-assessment Programme.

2.2 Each GMP national inspection service should use this document as the basis for developing its own quality system, so that inspection activities within each inspection service are carried out in accordance with a system compatible with those of the other member states.

3. Scope

3.1 This document specifies the quality system requirements for national pharmaceutical inspection services concerned with good manufacturing practice.

3.2 Where wholesale inspections are required by national legislation to be carried out by GMP national pharmaceutical inspection service, this document specifies the quality system requirements for national pharmaceutical inspection services concerned with good wholesale distribution practice of medicinal products.

3.3 The quality system should include all activities involved in the inspection process.

4. Definitions

4.1 Quality system:

The sum of all that is necessary to implement an organisation’s quality policy and meet quality objectives. It includes organisation structure, responsibilities, procedures, systems, processes and resources. Typically these features will be addressed in different kinds of documents as the quality manual and documented procedures, modus operandi.

4.2 Quality:

The totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs.

4.3 Pharmaceutical Inspectorate:

The national body responsible for co-ordinating and carrying out GMP inspections, including inspections of pharmaceutical manufacturers and/or wholesale distributors. If relevant, this could include making decisions concerning the issue or withdrawal of establishment licences or authorisations for their activities, the issue or withdrawal of GMP certificates, providing advice and handling suspected quality defects.
4.4 Licence:

For the purposes of this document, a licence is defined as an authorisation to manufacture or distribute medicinal products.

5. Quality Manual

5.1 The pharmaceutical inspectorate shall prepare and maintain a quality manual covering the elements described in this document. It is for each pharmaceutical inspectorate to decide on the format and style of their quality manual, but it must include, or make reference to, the quality system procedures which define the activities of the Inspectorate and the arrangements for maintaining the quality system. The reference used to complete it (as ISO or EN norms) must be quoted too.

6. Administrative Structure

6.1 The structure, membership and operation of the GMP pharmaceutical inspectorate shall be such as to enable it to meet the objectives of quality management and to ensure that impartiality is safeguarded.

6.2 The personnel of the inspection service, including sub-contracted personnel and experts, shall be free from any commercial, financial and other pressures which might affect their judgement and freedom to act. The pharmaceutical inspectorate shall ensure that persons or organisations external to the inspection organisation cannot influence the result of inspections. The system for obtaining fees should not improperly influence the inspection procedure. Rules for deontology, ethic and conflict of interests should be clearly defined.

6.3 The relationship of the pharmaceutical inspectorate to other agencies and to other organisations within and outside the Inspectorate shall be described where relevant.

6.4 The pharmaceutical inspectorate shall implement a policy which distinguishes between the process of inspection and that of issuing a GMP manufacturing authorisation.

6.5 Where relevant, the pharmaceutical inspectorate shall implement a policy which distinguishes between the process of inspection and that of providing an advisory service to clients. This service should be of benefit to all of industry and not solely to individual organisations.

7. Organisation and Management

7.1 Senior management of the pharmaceutical inspectorate shall make a formal commitment to the recommended principles embodied in this document by ensuring that the quality policy of the Inspectorate is documented, that it is relevant to the objectives of that organisation and that it is implemented.

7.2 The responsibility, authority and reporting structure of the pharmaceutical inspectorate shall be clearly defined and documented. The structure shall be defined in organisation charts and shall be supported by written job descriptions for each member of staff.

7.3 There shall be nominated an appropriately qualified and experienced person or persons with responsibility to carry out the quality assurance function, including implementing and maintaining the quality system. This person shall have direct access to senior management.
7.4 Senior management of the competent authority shall ensure that the pharmaceutical inspectorate has sufficient resources at all levels to enable it to meet its objectives effectively and efficiently. The senior management of the pharmaceutical inspectorate shall ensure that all personnel are competent and qualified to carry out their assigned duties and that they receive appropriate training. Such training shall be documented and its effectiveness assessed.

7.5 There shall be a system for periodic management review of the quality system. Such reviews shall be documented and records shall be retained for a defined period.

8. **Documentation and Change Control**

8.1 The pharmaceutical inspectorate shall establish and maintain a system for the control of all documentation relating to the inspection system. This shall include policies, procedures, guidelines and any documents of external origin such as regulations and directives which may direct the activities of the Inspectorate or influence the quality of its operations.

8.2 The document control system shall ensure that documents are authorised by appropriate persons prior to issue and that only current versions are held by nominated individuals. A record of all relevant documents and document holders shall be maintained. The system shall ensure that superseded documents are withdrawn from use. Superseded documents shall be retained for an appropriate and defined period.

8.3 The documentation system shall ensure that any changes to documents are made in a controlled manner and are properly authorised. There shall be a means of identifying changes in individual documents.

9. **Records**

9.1 The pharmaceutical inspectorate shall establish and maintain a system of records relating to its activities which complies with any existing regulations. If relevant, the system shall include documents received from licence applicants and licence holders as appropriate.

9.2 Records shall provide detailed information about the planning of inspections, the way in which each inspection was applied, a description of the inspection process, follow-up activities and recommendations to the body responsible for issuing licences.

9.3 All records shall be handled in such a way as to prevent their damage or loss and shall be retained for an adequate period consistent with any legal requirements. All records shall be maintained in confidence to the inspected party unless otherwise required under freedom of information legislation, or unless required under exchange of information procedures and arrangements between national pharmaceutical inspectorates, the EU/EEA, the EMEA and Mutual Recognition Agreement (MRA) or PECA partners.

10. **Inspection Procedures**

10.1 The pharmaceutical inspectorate shall conduct repeated inspections of manufacturers and/or wholesale distributors and shall issue inspection reports in accordance with national or European Community requirements as appropriate.
10.2 The pharmaceutical inspectorate shall have the documented procedures and resources to enable inspection of manufacturing and wholesale distribution operations to be carried out in accordance with the official guidelines and national legislation and in accordance with a formal inspection plan. All instructions, standards or written procedures, worksheets, check lists and reference data relevant to the work of the pharmaceutical inspectorate shall be maintained up-to-date and be readily available to staff.

10.3 When more than one inspector is involved in an inspection, a lead inspector shall be appointed to co-ordinate inspection activities. The inspection report shall normally be prepared by the lead inspector and shall be agreed by all participating inspectors.

10.4 The inspection report format should be in compliance with the European model.

10.5 The report should be sent to the responsible person of the inspected structure (preferably the qualified person). The lead inspector and all concerned inspectors should participate in assessing the reply.

10.6 Observations and/or data obtained in the course of inspections shall be recorded in a timely manner to prevent loss of relevant information.

10.7 Completed inspections shall be reviewed to ensure that requirements are met.

11. Inspection Resources

11.1 Personnel

11.1.1 The pharmaceutical inspectorate shall possess the required personnel, expertise and other resources to perform inspections of manufacturers and/ or wholesale distributors to determine their compliance with the principles and guidelines of current good practices and with the relevant legislation.

11.1.2 The staff responsible for inspections shall have appropriate qualifications, training, experience and knowledge of the inspection process. They shall have the ability to make professional judgements as to the conformance of the inspected party with the requirements of good practices and the relevant legislation and be able to apply an appropriate degree of risk assessment. They shall have knowledge of current technology, including computerised systems and information technology.

11.1.3 The pharmaceutical inspectorate shall establish a documented system for recruiting and training its personnel and shall carry out a regular review of the training received and the training needs for each member of staff. Individual training and qualification records shall be maintained.

11.2 Resources and equipment

11.2.1 The pharmaceutical inspectorate shall have available the necessary resources and equipment to enable it to carry out its obligations effectively and efficiently.

11.3 Risk management

11.3.1 The pharmaceutical inspectorate should implement risk management for assigning resources and prioritizing tasks and activities to carry out its obligations.( e.g. planning of inspections).

11.3.2 The pharmaceutical inspectorate should also implement risk approach in the conducting of inspection.
12. Internal Audit

12.1 The pharmaceutical inspectorate shall carry out and document periodic internal audits of its operations to assess compliance with the requirements of the quality system. Results of internal audits and associated corrective actions shall be reviewed as part of the management review process.

12.2 Internal audit processes and documents, auditors qualifications should be clearly defined (e.g. reference to ISO 19011 : 2002).

12.3 Internal audit records shall be retained for a defined period.

13. Quality Improvement and Corrective/Preventive Action

13.1 Quality indicators:

13.1.1 The pharmaceutical inspectorate should establish and maintain quality indicators related to its activities notably in the area of timeframe mentioned in existing EU or national regulations (e.g. licensing system for manufacturing or marketing authorizations) and/ or documentation (e.g. writing reports).

13.1.2 Quality indicators should be reviewed as part of the management review process.

13.2 Corrective/ preventive action:

13.2.1 The pharmaceutical inspectorate shall establish and maintain a procedure for the investigation of non-compliances with the quality system which are identified through internal or external audit of its activities. The procedure shall include the prescribing, implementation and verification of corrective action. The procedure shall cover also corrective actions arising from the investigation of complaints and other observations relating to the activities of the Inspectorate.

13.2.2 The system shall include a description of the steps to be taken in assessing the need for quality improvement and preventive action.

13.2.3 Corrective and preventive actions shall be documented and records shall be retained for a defined period.

14. Complaints

14.1 The pharmaceutical inspectorate shall establish and maintain a procedure for dealing with complaints relating to its activities, or those of its personnel, and any contracted persons or organisations. The procedure shall describe the application and verification of corrective action arising from the investigation of complaints.

14.2 Records shall be maintained of all complaints received and actions taken and shall be retained for a defined period.

15. Issue and Withdrawal of Licences and GMP Certificates

15.1 The pharmaceutical inspectorate shall establish and maintain a system for the issue and withdrawal of licences and GMP certificates, or for advising about the issue and withdrawal of licences and GMP certificates, as appropriate.
15.2 Licence and GMP certificate applications shall be assessed and determined in a timely manner and within any time limits imposed by national or European Community requirements. Where time limits are imposed, inspection activities shall be included in the total time taken to determine the application.

15.3 There shall be a documented system for taking appropriate action against a licence and/or a GMP certificate notably in the event of an adverse inspection report and for notifying other Member States. The system shall be based on QRM and include descriptions of the actions available to the Inspectorate; such actions may include suspension, variation or revocation of the licence and/or the GMP certificate(s). There shall be a system for assessing compliance of an organisation with the imposed licensing action.

15.4 The system shall include a description of the appeals procedure available to licence holders.

15.5 If the licensing system is not part of the pharmaceutical inspectorate, the latter should establish and maintain a defined liaison with it to obtain and guarantee the objectives mentioned above.

Marketing authorisation

15.6 The pharmaceutical inspectorate should establish and maintain a defined liaison with units responsible for marketing authorisation in order to facilitate actions against marketing authorisation following an inspection, if appropriate.

15.7 Other Member states should be informed with such actions, if appropriate.

16. Handling Suspected Quality Defects and Rapid Alert System

16.1 The pharmaceutical inspectorate shall establish and maintain a system for handling of reports of suspected quality defects in medicinal products as defined in the related Community procedure. This system shall be based on QRM.

16.2 The pharmaceutical inspectorate shall establish and maintain a system for issuing Rapid Alerts as defined in the related Community procedure.

16.3 The pharmaceutical inspectorate shall establish and maintain an updated list of all performed recalls.

16.4 If the organization in charge of handling suspected quality defects and the rapid alert system is not part of the pharmaceutical inspectorate, the latter should establish and maintain a defined liaison with it to obtain and guarantee the objectives mentioned above.

17. Liaison with the Official Medicines Control Laboratory (OMCL)

17.1 The pharmaceutical inspectorate should establish and maintain a defined liaison with the OMCL(s) of its own MS in order to exchange information concerning the quality of medicines on the national market. In particular, a validated SOP shall define sampling processes for starting materials and medicinal products.
18. Sub-Contracting and Assessing

18.1 The pharmaceutical inspectorate shall normally carry out the inspections for which it is responsible and whilst it may sub-contract some of its work it cannot sub-contract any of its responsibility. Sub-contracted personnel or experts may be employed as part of an inspection team to assist or advise in a technical capacity, but that team shall normally be led by a GMP lead inspector. Sub-contracted personnel shall be bound by the requirements of the quality system and there shall be a written contractual agreement between the parties.

18.2 Persons or organisations to whom inspection activities are contracted out and experts shall be free from any commercial or financial pressures which might affect their freedom to act. They should follow defined rules to avoid conflict of interests and regarding ethic and deontology. Senior management of the pharmaceutical inspectorate shall ensure that these persons are appropriately qualified and experienced and that they are independent of any organisations which they might be asked to inspect.

19. Publications

19.1 The pharmaceutical inspectorate should have at its disposal an updated list of licensed manufacturers and/or wholesale distributors. The list shall be made available on demand made by authorised bodies.
Procedures Related to Rapid Alerts

Handling of Reports of Suspected Quality Defects in Medicinal Products

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<tbody>
<tr>
<td>Date of adoption</td>
<td>31 January 2010</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>1 August 2010</td>
</tr>
<tr>
<td>Supersedes</td>
<td>Version in force from 1 September 2003</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>The scope was extended to include active substances/ active pharmaceutical ingredients and falsified medicines</td>
</tr>
<tr>
<td>Notes</td>
<td>None</td>
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Handling of Reports of Suspected Quality Defects in Medicinal Products

1. **Scope**

This guidance covers the handling of reports of suspected quality defects in medicinal products for humans and animals made to a Competent Authority before, if necessary, a rapid alert is transmitted. It recommends the elements of a procedure for receiving, assessing and categorising reports of suspected defective products that necessarily precedes a rapid alert.

2. **Introduction**

2.1. Discussion at the GMP/ GDP Inspectors Working Group and elsewhere has indicated the need to harmonise the handling of reports of suspected quality defects in medicinal products and confirm mutual confidence in Member States’ procedures for assessing the need to transmit a rapid alert of a quality defect.

2.2. Holders of an authorisation under Article 40 of Directive 2001/83/EC and under Article 44 of Directive 2001/82/EC (i.e. manufacturers and importers of medicinal products) are obliged under Article 13 of Directive 2003/94/EC or Article 13 of Directive 91/412/EEC and GMP Guide Chapter 8.8 to report to their Competent Authority any defect in a medicinal product handled under their authorisation that could result in a recall or abnormal restriction in supply. This includes possibly faulty manufacture, product deterioration, detection of falsified medicines or any other serious quality problems with a product. It is normally the Qualified Person who has this responsibility.

Reports of suspected defects may also be sent to the authorities by other competent authorities, health professionals, wholesale dealers and members of the general public. In addition, a report of an adverse drug reaction may in fact be due to a defect in the quality of the product concerned.

Official Medicines Control Laboratories may also report to their competent authorities confirmed out of specification results from testing medicinal products on the market requiring further assessment.

2.3. Member States are obliged to take all appropriate measures to ensure that a medicinal products is withdrawn from the market if it proves to be harmful under normal conditions of use, if its composition is not as declared or if the controls on the finished product or during the manufacturing process or other requirement of the manufacturing authorisation has not been fulfilled [Article 117 of Directive 2001/83/EC and Article 83 of Directive 2001/82/EC].

2.4. Each Competent Authority should have a written procedure that covers the receipt and handling of notifications of suspected defective products and batch recalls from companies or health professionals both during and outside normal working hours.
2.5. It is normally the responsibility of the company to recall a batch and to notify customers accordingly. It is normally the responsibility of the Competent Authority to notify other authorities of the recall. Responsibilities for notifying health professionals, media and the general public may vary between member states.

3. Definitions

*Suspected defective product.* A medicinal product about which a report has been received suggesting that it is not of the correct quality, as defined by its Marketing Authorisation.

*Batch recall.* The action of withdrawing a batch from the distribution chain and users. A batch recall may be partial, in that the batch is only withdrawn from selected distributors or users.

*Rapid Alert.* An urgent notification from one competent authority to other authorities that a batch recall has been instituted in the country originating the rapid alert. The procedure for handling rapid alerts and recalls arising from quality defects is part of the Compilation of Community Procedures.

4. Handling Process

4.1 Aim

To record and assess, during and outside office hours, reports of suspected defective products and to implement action with appropriate urgency.

4.2 Process Steps

4.2.1. Contact details for reporting suspected defective medicinal products to the Competent Authority should be made widely known and readily available to those likely to need to make a report. This would include manufacturers and marketing authorisation holders and may also include wholesalers, hospitals, pharmacists, veterinary practitioners and local health authorities.

A dedicated, continuously manned telephone line is preferred. Arrangements should be made to divert calls if necessary during out-of-office hours. If other means such as fax or e-mail are used they should be monitored frequently, including during out-of-office hours.

4.2.2. Every contact should be recorded, using a standard format for recording information. The first informant is unlikely to have all the required information so it is most important that a contact is agreed from whom further information may be obtained. A registered file should be established for each suspected defect to collect information as it becomes available.

4.2.3. The report should be referred with minimum delay to a person(s) able to make an initial professional assessment of the nature, extent and urgency of possible public health and animal health risk. A target time should be set for reports to be referred to this person, normally less than one hour. It may be possible to give guidance to the person receiving out-of-hours reports on the nature of reports which must be relayed to the professional assessor before the next routine working day.
4.2.4. The initial professional assessment should include the following considerations:

- risk to health of an individual (human or animal) if the suspected defect is real (consider risk to vulnerable patients as well as normal individuals, risk of not receiving the correct medication, risk from incorrect dosage (consider the therapeutic index), long-term risk as well as immediate risk (e.g. if a complete dispensed container is faulty the impact on the individual will be cumulative, risk to persons administrating a defective veterinary medicinal product, risk to the consumer of animal foodstuff in view of possible residues in the foodstuff):

- probability that the defect is real and occurs in the medicine supplied by the manufacturer or importer (e.g. not a clinical effect with a different cause, not a defect introduced at the time of dispensing).

- in the case of suspicion of defective vaccines (cross contamination with a virus), risk of distorting the analysis in national programmes against certain viral diseases.

4.2.5. At this stage it will be decided whether the potential hazard to health is such that extraordinary measures must be taken (including the convening of an emergency action group out-of-office hours) or whether further consideration may be left for normal office hours.

4.2.6. Further professional assessment of the risk from the product should involve discussion with the manufacturer or importer and include consideration of:

- any other reports which may be related;

- the distribution of the batch (e.g. restricted to known hospitals, widespread through wholesalers);

- date of first distribution and last distribution;

- any remaining stock with the manufacturer or importer;

- probability that other batches are affected in the same way, and their distribution.

4.2.7. If a recall is being considered extremely important issues to consider include:

- possibility of an out-of-stock situation;

- availability of alternative products;

- clinical effect of a disruption in supply.

**Note:** No supply of a product may be worse than use of product with a suspected deficiency.

4.2.8. Direct personal contacts are important, especially with the person making the report, the person co-ordinating action for the company (usually the QP), the inspector familiar with the manufacturer or importer and persons responsible for vigilance within the Competent Authority.

It is often helpful in detailed discussions if communications are between professional equivalents, e.g. medical assessor with medical staff of the company, inspectors with QPs or production staff, analytical assessors with QC staff, etc.

All information obtained verbally should be confirmed in writing.
4.3 Samples

Wherever possible the sample involved in the defect report should be obtained by the Competent Authority. It should normally be examined by an Official Medicines Control Laboratory as agreed by the Competent Authority. In certain cases samples should be provided to the company for examination under full supervision of the Competent Authority. Results should always be made available to the company.

*Note:* A company should have instructions for release of retained samples in order not to have all of them used up during an emergency situation other than with consent from the Competent Authority.

4.4 Inspection

The inspector normally associated with the manufacturing or importing site should be made aware of the report and may comment on general GMP compliance and what related products made.

On-site inspection may be required to assess batch records of the product concerned, plant records and records of other batches or products which could also be affected.

Samples may be taken of the batch concerned, related batches and related starting materials. When considering taking material from the company’s retained samples, consideration must be given to the quantity available and all tests which may be required for further investigations. These may be prescribed by the marketing authorisation or national requirements. This could also be applied to the European Agency.

4.5 Preparing a Decision

4.5.1. Having considered all the available information, including the need to make a decision without waiting for full information to be available because of the potential risk to public health, a decision will be taken on appropriate action, which may be one or more of the following according to national procedures:

- filing without follow-up (no further action);
- further investigation;
- quarantine of remaining stock at manufacturer and quarantine or recall at wholesalers either while further investigation occurs or to prevent further distribution even if a full recall is not required;
- GMP measures to avoid a recurrence;
- distribution of a ‘caution in use’ notice to concerned health professionals;
- notification of the batch recall to selected health professionals (e.g. particular hospitals, clinics, dentists);
- notification of the batch recall to all health professionals (e.g. including all hospitals, doctors, community pharmacies, veterinary practitioners etc.);
- notification of the batch recall through the media;
- publication on the competent authority website, newsletter or similar.
- an assessment should be made if other batches of the same products or other products could be affected the same GMP deficiency.
The exact wording of any notification should be checked and if possible agreed with the company. Particular attention should be paid to check the batch number(s), expiry dates and product name and strength. Advice should be given on where further information may be obtained (normally from the company).

The distribution of the notification to interested parties within the authorities should be agreed. This may include national Ministers and other government departments, government press officers and, by means of a Rapid Alert, authorities and organisations in other countries (EEA, MRA Partners, PIC/S participating authorities, WHO, others).

As far as possible standard formats, wording and distribution lists should be used for the notifications with the aim of ease of understanding by the recipient and lack of ambiguity.

4.6 Validating the Decision

According to the national Competent Authority procedures, approval should be obtained for the proposed action.

4.7 Implementing the Decision

Refer to national procedures and the Procedure for Handling Rapid Alerts from Quality Defects.

4.8 Follow-Up

4.8.1. There should be consideration of what if any action to take concerning the Marketing or Manufacturing Authorisations and their holders.

4.8.2. The Inspectorate should assess the follow-up actions by the company, including the reconciliation of issued, returned and remaining stocks, the investigation into the cause of the defect and actions to prevent a repetition.

4.8.3. Completion of any follow-up actions should be checked, for example completing and organising records and archiving according to national procedures.

5. Quality Assurance

5.1. All procedures should be documented and maintained up to date.

5.2. Contact lists for officials and companies should be maintained up-to-date and should be verified at intervals (e.g. a rolling programme of annual checks of company contacts, possibly as part of GMP inspections).

5.3. All staff who could be involved in receiving a report of a suspected defective product or handling a Rapid Alert should be trained in the relevant procedures and have access to a copy of the SOPs and report forms wherever they may be required to act (including at home if they are on call outside-office hours).

5.4. It is particularly important that those procedures which may need to be followed by staff not routinely involved (e.g. called upon as a reserve) and/or required to be involved when away from their office should be detailed and easy to follow.
Procedures Related to Rapid Alerts

Procedure for Handling Rapid Alerts Arising from Quality Defects

Table of contents:

- Scope
- Introduction
- Criteria for Issuing a Rapid Alert
- Issue of a Rapid Alert Notification
- Fraud and Falsified Products
- Follow-up Action
- Further use of Rapid Alert Contact List
- Appendices

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<tr>
<td>Reason for revision</td>
<td>Transmission of notifications changed from fax to email, Class I and II defects to be circulated to all contacts on notification list. The scope was extended to include active substances/active pharmaceutical ingredients and investigational medicinal products</td>
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<td>Pharmacovigilance or medical device alerts are not included within the scope of this procedure</td>
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Procedure for Handling Rapid Alerts Arising from Quality Defects

1. Scope

This procedure covers the transmission of information when urgent action is required to protect public or animal health by means of a rapid alert relating to the recall of medicinal products, which have quality defects or which are falsified, between Competent Authorities responsible for human and veterinary medicinal products in the European Economic Area (EEA) (the "Member States"), in EU acceding countries, MRA countries, authorities participating in PIC/S, the European Commission and international organisations (Council of Europe/EDQM, WHO). It may also be extended to authorities in countries with which the Community has made appropriate arrangements on GMP. The procedure may be used also for transmission of other information such as cautions-in-use, product withdrawals for safety reasons or for follow-up messages to any of the above listed categories. This procedure covers both human and veterinary medicinal products and operates within the scope of the relevant Two Way Alert programmes established between the Community and MRA partners.

The procedure may also be used to notify quality defects, counterfeit or fraud in active pharmaceutical ingredients or investigational medicinal products when deemed relevant by the issuing authority.

Pharmacovigilance or Medical Device alerts are not included within the scope of this procedure.

2. Introduction

2.1 In order to protect public health and animal health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product during its marketing period or an investigational product during clinical trials.

2.2 Each holder of an authorisation referred to in Article 40 of Directive 2001/83/EC (for medicinal products for human use), Article 13 of Directive 2001/20/EC (for investigational medicinal products) or Article 44 of Directive 2001/82/EC (for veterinary medicinal products) is required by Article 13 of Directive 2003/94/EC or Article 13 of Directive 91/412/EEC (for veterinary medicinal products) to implement an effective procedure for the recall of defective products. The authorisation holder is required to notify the relevant Competent Authority of any defect that could result in a recall and indicate, as far as possible, the countries of destination of the defective product.

2.3 In addition, for centrally authorised products Council Regulation EC/726/2004, Art. 16(2) or Article 41(4) (for veterinary products) the marketing authorisation holder is obliged to keep the European Medicines Agency informed of certain new information (e.g. restrictions of supply).

2.4 Each Competent Authority should have a written procedure for the issue, receipt and handling of notifications of defective products, batch recalls and other rapid alerts during and outside normal working hours.
2.5 The Competent Authority of each Member State should assist the authorisation holder in the recall process, as appropriate, and monitor its effectiveness. The Competent Authority should ensure that information concerning the recall of medicinal products is notified rapidly to other Member States, if the nature of the defect presents a serious risk to public health. This information should be transmitted by means of the "Rapid Alert System”.

3. Criteria for Issuing a Rapid Alert

3.1 The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission. To ensure its effectiveness, the system must not be saturated by the transmission of less urgent information. In each case a professional assessment must be made of the seriousness of the defect, its potential for causing harm to the patient or (in the case of a veterinary product) harm to animals, consumers, operators and the environment, and the likely distribution of the affected batch(es). Appendix 1 provides guidance on the classification of the urgency of the recall of defective medicinal products.

3.2 **Class I** defects are potentially life threatening. A rapid alert notification must be sent to all contacts of the rapid alert notification list irrespective of whether or not the batch was exported to that country.

3.3 **Class II** defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent to all contacts of the rapid alert notification list as it might be difficult to know where a batch has been distributed. If the product distribution is known, the notification should be only sent to the contacts concerned.

3.4 **Class III** defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons. These are not normally notified through the Rapid Alert System.

3.5 Where appropriate, the rapid alert system may be used for notification to authorities concerned of the recall of products or an embargo on the distribution of products following suspension or withdrawal of a manufacturing / wholesale authorisation.

4. Issue of a Rapid Alert Notification

**Responsibility**

4.1 For a batch manufactured in a Member State, or a batch manufactured in a third country and imported into the EEA, which is the subject of a national (including mutually recognised or decentralised) marketing authorisation, the Competent Authority of the Member State in which the defect was first identified should investigate the defect and issue the rapid alert.

4.2 In the case of a centrally authorised product, and in the exceptional case of a product that has both a centralised and a national authorisation, the Competent Authority of the Member State in which the defect was first identified should lead the investigation of the defect and issue the rapid alert (the issuing authority). The alert should include a recommendation on proposed action for all affected authorities.
When time allows, the content of the proposed action should be agreed with the supervisory authority, the European Medicines Agency and the CxMP rapporteur. In some circumstances and especially when the Supervisory Authority has conducted all the investigations, the Member State in which the defect was first identified may delegate to the Supervisory Authority the issuing of the Rapid Alert. When, due to the urgency of the defect there is not sufficient time to develop a harmonised proposed action, this section of the Rapid alert notification should inform all recipients that the European Medicines Agency will co-ordinate further action in co-operation with the relevant Supervisory Authority, in accordance with the Agency’s Crisis Management Procedures and that harmonised follow-up actions will be transmitted when ready.

4.3 In the case of parallel distribution of a centrally authorised product and where no repackaging is carried out, the procedure described under 4.2 applies. This procedure also applies if the defect resulted from a repackaging operation. Where repackaging is carried out but the defect results from the original manufacturing process, the procedure described under 4.2 still applies, but the rapid alert should include descriptions of the different packaging in which the product might appear (for example different language versions and pack sizes) where this information is available from the European Medicines Agency.

4.4 In the case of a parallel import, the Competent Authority of the Member State in which the defect was first identified should issue the rapid alert.

**Format of the rapid alert and its transmission**

4.5 A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2. The form should be completed clearly in English. The notification and relevant documents should be sent to the rapid alert contact list by electronic mail. The contact list and any relevant documents should be attached to the notification.

The electronic mail message should use a unique subject line to identify the rapid alert and any follow-up messages. The subject line should consist of the following:

RapidAlert; [Qdefect / Counterfeit / Fraud], Class [ I / II]; Product [Name / INN], Action [Recall / No Recall / Follow-up], Rapid alert reference number. (For example RapidAlert; Qdefect; I, ProductX; Follow-up,CH/I/07/01 ).

The rapid alert should be given a unique reference number with the following format:
Country code (country where the original alert was issued)/Region or Authority code (where applicable)/classification/sequential number/correspondence number. (For example ES/II/05/02 would indicate a class II rapid alert initiated by Spain, being the 5th rapid alert initiated by Spain and that it is the second correspondence regarding this rapid alert.)

4.6 Transmission of a Class I rapid alert must be concurrent with the national action. Whenever feasible, transmission of a Class II rapid alert should be concurrent with the national action but in all cases should be within 24 hours of the national notification.

In the case of a Class I notification, it may be necessary to alert authorities in different time zones in addition by telephone.

When an authority issues a further rapid alert for a batch, the field 18 in the form in Appendix 2 “Detail of Defect/Reason for recall” should begin with the text: “Rapid Alert following original rapid alert #ref. no.#”. 
Rapid alert contact list

4.7 The European Medicines Agency maintains the contact list for the rapid alert notifications of the competent authorities covered by Section 1. There is normally one contact per authority nominated by each member state. Changes to contact names or details must be notified to the European Medicines Agency (qdefect@ema.europa.eu) and are circulated immediately to the entire list by electronic mail. Contact details include telephone and fax numbers, electronic mail address, which should be monitored at all times.

5. Fraud and Falsified Products

The Rapid Alert System should be used to notify competent authorities of the possible presence in the legal distribution network of falsified products or those resulting from fraud in manufacture, packaging, distribution or promotion and products containing falsified starting materials.

The Competent Authority of the Member State or MRA partner in which the fraud or falsification was first detected should issue the notification. The format for the rapid alert notification in Appendix 2 may be used, but the heading on the document should make clear that the notification relates to fraud or to a falsified product and sufficient information should be provided under "details of defect" to enable it to be identified. Notification should be sent to the entire contact list.

6. Follow-Up Action

Each Competent Authority should have a written procedure to describe follow-up action to a rapid alert notification. The Competent Authority of each Member State and MRA partner to which a recalled product was exported should monitor the conduct and effectiveness of any national recall that it initiates as a result of the rapid alert notification.

The relevant Supervisory Authority should investigate the circumstances that led to the distribution of the defective product and ensure that any necessary corrective action is taken by the manufacturer and marketing authorisation holder as appropriate.

The European Medicines Agency should co-ordinate follow-up action for recalls of centrally authorised products.

All follow-up actions transmitted through the Rapid Alert System should use the form for Follow-up and non-urgent messages for Quality Defects detailed in Appendix 3 to separate it from Rapid Alerts. It should have a reference number linking it to the original Rapid alert following the same format as described above.

7. Further Use of Rapid Alert Contact List

Although the contact list for rapid alert notifications shall be only used for the transmission of notification falling in the scope of this procedure and the GMP non-compliance procedure, in exceptional cases, if deemed relevant by the competent authority, the list may be used for the communication of other important and urgent information related to pharmaceutical products. These messages should clearly identify the subject and whether they are for information or action. For example, the European Medicines Agency disseminates urgent information from its scientific committees in this way.
8. Appendices

8.1 Appendix 1: Classification of Rapid Alerts
8.2 Appendix 2: Format for Rapid Alert Notification of a Quality Defect
8.3 Appendix 3: Format for Follow-up and non-urgent information for Quality Defects
Appendix 1

Rapid Alert System: Classification of Urgency of Defective Medicinal Product Alerts

CLASS I

Class I defects are potentially life threatening or could cause a serious risk to health. These must be notified through the Rapid Alert System in all cases.

Examples:
- Wrong product (label and contents are different products)
- Correct product but wrong strength, with serious medical consequences
- Microbial contamination of sterile injectable or ophthalmic product
- Chemical contamination with serious medical consequences
- Mix-up of some products (rogues) with more than one container involved
- Wrong active ingredient in a multi-component product, with serious medical consequences.

CLASS II

Class II defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent to all contacts of the rapid alert notification list as it might be difficult to know where a batch has been distributed. If the product distribution is known, the notification should be only sent to the contacts concerned.

Examples:
- Mislabelling, e.g. wrong or missing text or figures
- Missing or incorrect information (leaflets or inserts)
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/physical contamination (significant impurities, cross-contamination, particulates)
- Mix up of products in containers (rogues)
- Non-compliance with specification (e.g. assay, stability, fill/weight)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child-resistant containers, potent products).

CLASS III

Class III defects may not pose a significant hazard to health, but withdrawal may have been initiated for other reasons. If deemed relevant by the issuing authority, the rapid alert system may be used.

Examples:
- Faulty packaging, e.g. wrong or missing batch number or expiry date
- Faulty closure
- Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter
## Appendix 2

### IMPORTANT – DELIVER IMMEDIATELY

**Rapid Alert Notification of a Quality Defect / Recall**

<table>
<thead>
<tr>
<th>Reference Number</th>
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</table>

<table>
<thead>
<tr>
<th>[add letter head of sender]</th>
</tr>
</thead>
</table>

1. **To:**  
   (see list attached, if more than one)

2. **Product Recall Class of Defect:**  
   (circle one)

3. **Falsification / Fraud (specify)**

4. **Product:**

5. **Marketing Authorisation Number:**  
   *For use in humans/animals (delete as required)*

6. **Brand/Trade Name:**

7. **INN or Generic Name:**

8. **Dosage Form:**

9. **Strength:**

10. **Batch number (and bulk, if different):**

11. **Expiry Date:**

12. **Pack size and Presentation:**

13. **Date Manufactured:**  
   *

14. **Marketing Authorisation Holder:**  
   *

15. **Manufacturer†:**
   
   **Contact Person:**
   
   **Telephone:**

16. **Recalling Firm (if different):**
   
   **Contact Person:**
   
   **Telephone:**

17. **Recall Number Assigned (if available)**

18. **Details of Defect/Reason for Recall:**

19. **Information on distribution including exports (type of customer, e.g. hospitals):**  
   *

20. **Action taken by Issuing Authority:**

21. **Proposed Action:**

22. **From (Issuing Authority):**
   
   **23. Contact Person:**
   
   **Telephone:**

24. **Signed:**

25. **Date:**

26. **Time:**  
   *

* Information not required, when notified from outside EU.

† The holder of an authorisation referred to under Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC if different.

This is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us by telephone immediately and return it to us at the above address by mail. Thank you

***************
### Appendix 3

#### Follow-up and Non-urgent Information for Quality Defects

<table>
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<th>[add letter head of sender]</th>
</tr>
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</table>

1. **To:** (see list attached, if more than one)

<table>
<thead>
<tr>
<th>Recall Number Assigned:</th>
<th>National reference number (When applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a. National reference number</td>
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4. **Product:**  

<table>
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<tr>
<th>Product:</th>
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6. **Brand/Trade name:**  

<table>
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<tr>
<th>Brand/Trade name:</th>
</tr>
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</table>

8. **Dosage form:**  

<table>
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<th>Dosage form:</th>
</tr>
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</table>

14. **Marketing Authorisation holder:**  

<table>
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<th>Marketing Authorisation holder:</th>
</tr>
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</table>

15. **Manufacturer**:  

<table>
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<tr>
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</table>

16. **Contact Person:**  

<table>
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<th>Contact Person:</th>
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</thead>
</table>

17. **Subject title**  

| Add bulk message here |

22. **From (issuing Authority):**  

<table>
<thead>
<tr>
<th>From (issuing Authority):</th>
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</table>

23. **Contact person:**  

<table>
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<tr>
<th>Contact person:</th>
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</table>

24. **Signed:**  

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<th>Signed:</th>
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25. **Date:**  

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<th>Date:</th>
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</table>

26. **Time:**  

<table>
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<tr>
<th>Time:</th>
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1 The holder of an authorisation to under Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC, if different.
Procedures Related to GMP Inspections

Conduct of Inspections of Pharmaceutical Manufacturers or Importers

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- Introduction
- General Considerations on Inspections
- Inspection Planning and Preparation
- Inspection Steps
- Final Meeting
- Inspection Report
- Inspection Frequency
- Quality Management of the Inspector’s Activity
- Glossary of Terms

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<tr>
<td>Date of adoption</td>
<td>January 2010</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>[Immediately after publication. Annex on Active Pharmaceutical Substances within six months of publication.]</td>
</tr>
<tr>
<td>Supersedes</td>
<td>Version adopted in 2006</td>
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<td>Reason for revision</td>
<td>Annex on active substances/ active pharmaceutical ingredients added and main text updated in line with EU GMP Guide. A wording for the risk based approach to conducting inspections was added (Sections 3.1, 4.3, 7). Clarification concerning the scope and the application to inspections of importers</td>
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Conduct of Inspections of Pharmaceutical Manufacturers or Importers

1. Introduction

In line with Articles 42 and 111 of Directive 2001/83/EC and Article 46 and 80 of Directive 2001/82 inspections are performed at manufacturers and importers of medicinal products and in line with 15 of Directive 2001/20/EC inspections are performed at manufacturers and importers of investigational medicinal products.

In addition, Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC include provisions for inspections of manufacturers and importers of active substances used as starting materials.

This procedure is intended

The purpose of this document is to provide guidance on the conduct of inspections to harmonise inspection procedures, frequency of inspections and follow-up procedures thus ensuring a consistent approach to assessment and decision-making by Competent Authorities.

Chapters 2-9 of the main procedure are applicable to manufacturers, and where appropriate, to importers, of medicinal products, investigational medicinal products or active substances. The Annexes provide additional specific provisions:

Annex 1 includes specific provisions for product related inspections of manufacturers and importers of medicinal products.

Annex 2 includes specific provisions for inspections of manufacturers and importers of investigational medicinal products.

Annex 3 includes specific provisions for inspections of manufacturers and importers of active substances.

2. General Considerations on Inspections

2.1 The primary role of the inspector is the protection of public health in accordance with Community provisions.

2.2 The function of the inspector is to ensure adherence by manufacturers to GMP principles and guidelines including licensing provisions, marketing and manufacturing authorisations.

2.3 The primary goal for the inspector should be to determine whether the various elements within the quality assurance system are effective and suitable for achieving compliance with GMP principles. In addition the goal is to determine that medicinal products comply with their marketing authorisation.

2.4 Inspectors should strive to create a positive atmosphere during the inspection.

1 Following Article 46a of Directive 2001/83/EC and Article 50a of Directive 2001/82/EC for the purposes of these Directives the manufacture of active substances used as starting materials includes, inter alia, the import of active substances.
2.5 An inspector should be aware of his influence in decision making processes. The inspector should answer questions but avoid entering the role of a consultant.

2.6 The task of an inspector is not limited to the disclosure of faults, deficiencies and discrepancies. An inspection should normally include educational and motivating elements.

2.7 The wide diversity of facilities (both in terms of physical layout and management structure) together with the variety of products and production processes as well as analytical methods means that judgement by inspectors on-site of the degree of compliance with GMP is essential.

2.8 A consistent approach to evaluation of the GMP standard of companies is essential.

2.9 Inspections may disturb the normal work patterns within a company. Therefore, inspectors should take care not to put the product at risk, and should carry out their work in a careful and planned way.

2.10 Inspectors will, while conducting the inspection, have access to confidential information and should handle it with integrity and great care.

2.11 Prior to the inspection the inspector may consult with experts in a particular field.

3. Inspection Planning and Preparation

3.1 The Competent Authority should plan the succession of inspections in advance and elaborate a programme. This programme should ensure that the frequency of inspection of individual manufacturers can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner. The planning of inspections should be performed according to the Community Procedure “A model for risk based planning for inspections of pharmaceutical manufacturers”.

3.2 Preparation of inspections: prior to conducting an inspection the inspector(s) should familiarise themselves with the company to be inspected.

3.3 This may include:

- assessment of a site master file
- a review of the products manufactured/imported by the company
- a review of the reports from previous inspections
- a review of the follow-up actions (if any) arising from previous inspections
- familiarisation with the relevant aspects of the manufacturing authorisation including variations
- a review of any variations to the manufacturing authorisation
- a review of product recalls initiated since the previous inspection
- an examination of relevant product defects notified since the previous inspection
- a review of the analysis of any samples analysed by an OMCL since the previous inspection
• a review of any special standards or guidelines associated with the site to be inspected
• a review of relevant parts of the marketing authorisation of one or more selected products to be examined during the inspection
• a review of variations to marketing authorisations, applied for, granted and refused
• a review of information available on regulatory databases (EudraGMP, FDA warning letters etc)
• a review of significant changes to equipment, processes and key personal
• a review (or preparation) of aide-memoires for the specific inspection to be performed to avoid missing important aspects of GMP

It is recommended that inspectors prepare an inspection plan which may include:

• the objectives and the scope of the inspection, in the light of previous inspections
• identification of the people who are directly responsible for production and quality control / quality assurance. In cases where particular products and/or processes are to be inspected, the people directly responsible for these products and/or processes
• identification of the inspection team members and their respective roles, if more than one inspector is going to conduct the inspection
• the date and place, where the inspection is to be conducted
• identification of the organisational units to be inspected
• the expected time and duration for each major inspection activity (premises, processes etc.)
• samples (if any) to be taken
• the schedule for the final meeting
• the approximate schedule for the transmission of the inspection report

4. Inspection Steps

4.1 Announcement of inspection: Competent Authorities have the right to inspect at any time (including during shift work). Prior announcement of inspection may be given. By informing in advance the day/days for the inspection to take place and the length of time the inspector expects to be at the premises, the objectives of the inspection will be known to the company and the relevant personnel and documentation can more easily be made available.

4.2 Opening Meeting: The inspector should normally meet the management and the key personnel of the company to introduce himself and any accompanying official(s) or specialist(s) and to discuss his inspection plan (of course subject to unannounced modifications).

During the opening meeting the inspector should:

• outline the purpose and scope of the inspection
• review the management structure of the company (organization chart)
4.3 Inspection of the plant facilities: a rapid plant tour is often useful for familiarisation with the site and any major changes. Inspectors may follow the logical flow of the starting materials, goods inwards warehouse, through the production areas, quality control areas to the warehouse for released finished goods, taking into account the detailed guidelines of GMP. This could be followed by a detailed plant tour to determine whether the facilities and equipment are of suitable lay-out and design and whether the way in which they are used suits the intended operations. In some cases immediate inspection after arrival on site may be of value.

A risk based approach to conducting the inspection would be to look for signals during the a rapid plant tour or review of documents, which might indicate a problem with a product, process or system and the focus the inspection on these areas and as such keeping a flexible inspection plan. Likewise any identification of a high risk during the inspection could lead to a change in the inspection plan to go into more depth in the identified area.

Sometimes it is appropriate to concentrate effort in one department of the company if there are special problems or requirements, e.g. a department only producing sterile dosage forms or non sterile dosage forms. Relevant service areas should be included, e.g. water, steam and ventilation/dust extraction systems and engineering support.

During the inspection the inspector should always discuss observations as they arise with the key personnel, supervisors and operators in order to establish facts, indicate areas of concern and to assess the knowledge and competence of these personnel.

4.4 Review of documentation: the whole system of documentation, based on specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the different production, QC and distribution operations should be checked by examining particular examples both during use and after compilation into complete batch records.

4.5 A general GMP inspection will normally, in order to assess compliance with the terms and conditions of the manufacturing authorisation, include examination of the following:

- Conformity with good manufacturing practice
- Compliance with marketing authorisation
- Quality Management
- Personnel
- Premises and equipment
- Documentation
- Production
- Quality control
- Contract manufacture and analysis
- Complaints and product recall
- Self-inspection

4.6 Contract manufacture and analysis: operations contracted out and the responsibilities of the different parties should be clearly identified. The contract between the contract giver and the contract acceptor should be examined for compliance with the detailed guidelines of GMP.

4.7 Complaints and product recall: the system for recording and reviewing complaints as well as the system for recalling batches of medicinal products from within and outside the Member States should be examined during the inspection. Defect reports and recalls should be discussed.

4.8 Self-Inspection: the system for performing self-inspections in the company should be examined, although the reports themselves should not normally be read by the inspector.

4.9 A product-related inspection will normally, in order to assess compliance with the specifications of the marketing authorisation, include examination of the specific documentation relating to one or several completed batches of a specified product including:

- Standard operating procedures (SOPs)
- Product quality review
- Manufacturing formulae, records and instructions
- Specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products

4.10 For active substances used as starting materials: a check should also be made to ensure that the manufacturing authorisation holder is complying with the requirements of Article 46 (f) of Directive 2001/83/EC and Article 50 (f) of Directive 2001/82/EC as amended and has systems and procedures in place to only use as starting materials active substances that have been manufactured in accordance with the detailed guidance on Good Manufacturing Practices for active substances used as starting materials.

5. Final Meeting

5.1 When the inspection has been completed, the inspector should summarise the findings in the final meeting with representatives of the company, normally the technical management including the key personnel and preferably some or all of the senior management, if these are different from the key personnel.
5.2 The final meeting is a significant part of the inspection. The deficiencies observed during the inspection should be discussed. Their importance should also be discussed so that deadlines for remedial actions may be fixed.

5.3 Facts and objective evidence supporting the observations should preferably be agreed by the company. The company may if they so wish discuss initial proposals for remedial action.

5.4 As far as possible all relevant observations should be reported at this meeting so that the company can initiate the necessary corrective actions at the earliest possible date.

5.5 In case of serious deficiencies leading to possible serious risk for the patients, immediate action should be taken by the inspector.

6. Inspection Report

6.1 Inspection reports should be based on notes taken during the inspection. These notes should be clear and legible.

6.2 The inspection report should give a short description of the company and its activities, a description of the inspection itself and the inspector’s findings, observations and deficiencies.

6.3 The report should be in line with the Community format of the GMP inspection report.

6.4 The contents of the initial inspection report should be sent to the company for its comments to enable the report to be finalised within the relevant timeframe of the inspection request and to enable, if applicable, the issue of a GMP certificate within the statutory 90-day timeframe.

7. Inspection Frequency

The frequency of inspections may be based on the Community procedure “A model for risk based planning for inspections of pharmaceutical manufacturers”.

8. Quality Management of the Inspector’s Activity

8.1 Most inspectors work alone or, at most, in pairs. The possibility of a specialist participating in the inspection should be taken into consideration. There should be a system to monitor and control the inspector’s performance in order to ensure a correct and consistent approach on different occasions and between different inspectors. Monitoring should be planned to assess at least:

- the extent and depth of the inspection
- the ability to recognise deficiencies
- the assessment of the seriousness of deficiencies
- the action recommended
- the effectiveness with which the determined action is carried out

8.2 This quality system should include periodic joint visits with senior or specialist inspectors, and follow-up of recommendations and subsequent action.
9. Glossary of Terms

The definition of terms in the detailed guidelines published in Good Manufacturing Practice for Medicinal Products in the European Community, Volume 4 are applicable to this document. In addition, the following apply:

**Inspection**: On-site assessment of the compliance with the Community GMP principles performed by officials of Community Competent Authorities.

**General GMP inspections** (also termed regular, periodic, planned or routine) should be carried out before the authorisation referred to in Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC respectively, is granted and periodically afterwards as required to assess compliance with the terms and conditions of the manufacturing authorisation. This kind of inspection may also be necessary for a significant variation of the manufacturing authorisation and if there is a history of non-compliance. This includes follow up inspections to monitor the corrective actions required following the previous inspection.

On-site assessment of quality control laboratories is normally part of a GMP inspection.

**Product or process related inspections** (also termed pre-authorisation, pre-marketing, special, problem orientated) focus on the compliance of the manufacturer to the terms and conditions of the marketing authorisation and on the manufacture and documentation related to the product. It is also indicated when complaints and product recalls may concern one product or group of products or processing procedures (e.g. sterilisation, labelling, etc).

**Contract QC laboratories** are according to Article 20(b) of Directive 2001/83/EC or Article 24(b) of Directive 2001/82/EC or Article 13.1 of Directive 2001/20/EC subject to these inspections.

**Inspection report**: Report prepared by the official representing the Competent Authority stating whether the company inspected in general complies with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC and whether the manufacturer is acceptable for the products in question. The Community report format applies.
ANNEX 1

CONDUCT OF PRODUCT RELATED INSPECTIONS

Introduction

The purpose of this annex is to outline the extent to which the inspector may become involved in:

(a) the pre-marketing assessment of an application for a marketing authorisation and
(b) the assessment of compliance with the terms and conditions of a marketing authorisation granted in the European Community and in connection with Art. 58 of EC/726/2004.

The role of inspectors in the pre-marketing assessment of an application for a marketing authorisation

Verification of authorisations:

There should be a systematic procedure whereby the person responsible for assessment of an application consults the inspectorate. The extent of such consultation will depend upon the nature of the product, the manufacturing and control operations involved and on the quality of the application.

Consultation should include the following:

2. Verification that the appropriate authorisation is held where third country importation is proposed (Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC).
3. Verification that any Quality Control laboratory has been inspected and approved (Article 20(b) of Directive 2001/83/EC or Article 24(b) of Directive 2001/82/EC), including third country inspections.

The role of inspectors in assessing compliance with marketing authorisations

The inspector carries out an inspection of a manufacturer in order to assess the latter’s compliance with GMP. GMP includes ensuring that all manufacturing operations are in accordance with the relevant marketing authorisation (Art. 5 of Directive 2003/94/EC and 91/412/EEC). The inspector is also in a position to verify that the details relating to the manufacture and control of a product which were provided in the marketing authorisation application for that product, as modified and/or agreed during the assessment, are being adhered to in the manufacture of batches of that product for sale.

In certain circumstances, for example in relation to biological, biotechnological and other high technology products, it may be appropriate for the inspector to be accompanied by a relevant assessor. Alternatively, the inspector can be accompanied by the competent authority’s expert on the particular type of product or by an independent expert nominated by the competent authority.

The inspector should have all relevant sections from the marketing authorisation application to hand during the inspection for ready reference. This would be considerably facilitated by having an up to date summary of these sections readily available to the inspector.

Carrying out the inspection

Adherence to chemistry and pharmacy data supplied and approved in the marketing authorisation application.
The inspection should seek to verify, by means of examination of all relevant facilities, equipment and documents, that the information provided in the marketing authorisation application is being strictly adhered to. This examination might include:

(a) composition of the medicinal product  
(b) container  
(c) manufacturing formula  
(d) manufacturing process including in-process controls  
(e) source and nature of active ingredients  
(f) other ingredients  
(g) packaging materials  
(h) control tests on intermediate products  
(i) control tests on the finished product  
(j) labelling  
(k) any other data requested by assessors, including ongoing stability investigations.

In addition to this verification the following specific points should also be borne in mind:

**Samples**

Consideration should be given to taking the following samples:

(a) active ingredient (if material from more than one source is available, take a sample of each).  
(b) excipients (samples may be taken of non-pharmacopoeial and unusual materials).  
(c) finished product (sufficient to carry out full duplicate analysis and to meet the legal provisions of the Member State).  
(d) label  
(e) printed carton  
(f) data sheet

If finished product samples are to be taken directly from the market, the company should deliver relevant samples of

(a) active ingredients, and  
(b) excipients to the competent authority upon request.  
(c) any other samples requested by assessors.

All samples should be submitted for testing/review and, if indicated by the results, necessary follow up action should be taken.

**Copies of documents**

If necessary, copies of the finished product specification and method of analysis should be taken relating to the samples taken (if any) during the inspection.

If necessary, copies of the batch manufacturing document and of the finished product specification and method of analysis should be delivered to the competent authority upon request.
Complaints
Review any complaints relating to the product.

Amendments and variations
Following the granting of a marketing authorisation, the holder of a marketing authorisation may subsequently apply for amendments and variations to the original information to be approved by the competent authority.

Where such amendments and variations have been approved by the competent authority, the inspector should check that any master document to which an amendment or variation related, was altered to include the amendment or variation shortly after this was approved by the competent authority.

Review of documentation relating to the product
This should be carried out as set out in Section 12 of the main guideline. Documentation for a number of batches should be reviewed.

Section 6.9. of the Rules Governing Medicinal Products in the European Community, Volume 4, recommends that trend evaluation of analytical test results be carried out. If this has been done the evaluation should be reviewed.
ANNEX 2

CONDUCT OF INSPECTIONS FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE

Introduction

The purpose of this document is to define specific provisions for inspections of manufacturers of investigational medicinal products.

Scope

This guideline applies to the inspection of manufacturers, importers or analytical laboratories authorised in accordance with Article 13.1 of Directive 2001/20/EC by the competent authority of the Member State concerned. It also applies to inspections of manufacturers based in third countries where these are inspected in accordance with Article 15.4 of Directive 2001/20/EC. In both cases the inspection is carried out on behalf of the European Community and the outcome is recognised by all Member States.

Article 15.1 of Directive 2001/20/EC additionally refers to inspections carried out at other locations connected with any clinical trial and in some cases there will be overlap between Good Manufacturing and Good Clinical Practice. Examples include: release of investigational medicinal products, the generation of emergency code break systems in blinded clinical trials, preparation of investigational products at investigational sites including labelling, complaints, adverse events and recalls. Member States, particularly those that maintain separate inspectorates for these Good Practices, should ensure that overlap areas are identified, responsibilities understood and inspections performed by Inspectors with appropriate qualifications and training.

An inspection may be more product- or process-related when it focuses on the adherence by the manufacturer to the dossier of an investigational medicinal product submitted to the Competent Authority in order to obtain authorisation to conduct a clinical trial pursuant to Article 9.2 of Directive 2001/20/EC and on the manufacture and documentation related to the product or to a specific manufacturing process.

THIS ANNEX SHOULD BE READ IN CONJUNCTION WITH THE MAIN PROCEDURE. THE ANNEX PROVIDES ADDITIONAL INFORMATION ONLY

General Obligations

Member States

Member States should establish the legal and administrative framework within which Inspections relating to clinical trials including Good Manufacturing Practice (GMP) inspections as applied to investigational medicinal products operate.

Inspectors should be issued with an official means of identification, which includes reference to powers of entry, access to data and the collection of samples and documents for the purpose of inspection.

Member States should ensure that there are sufficient resources at all levels to effectively verify compliance with GMP for investigational medicinal products and that inspectors are competent and trained in order to carry out their tasks as referred to in the detailed guidelines for qualifications of GMP inspectors engaged in verifying GMP Compliance for Investigational Medicinal Products.
Inspectorates should adopt quality systems to ensure consistency of approach to inspection and evaluation of findings. Within the quality system inspectorates should develop detailed procedures in line with this guideline to suit national requirements and practices but consistent with procedures agreed at Community level such as report formats for the exchange of information.

General Considerations on Inspections of Investigational Medicinal Products

The primary goal for the inspector should be to determine whether the various elements within the quality assurance system are effective and suitable for achieving compliance with GMP principles. In addition, determining whether the investigational medicinal products comply with the dossiers submitted to the Competent Authority in order to obtain authorisation to conduct a clinical trial pursuant to Article 9.2 of Directive 2001/20/EC.

Product- or process-related inspections (also termed special or problem oriented) may be indicated to assess the adherence of the manufacturer to the investigational medicinal product dossier and the way the batch documentation is kept. It is also indicated when complaints, recalls or adverse event patterns may concern one product or group of products or processing procedures (e.g. sterilisation, labelling, etc). These inspections may be triggered by an Assessor raising questions during the evaluation of an application for authorisation to conduct a clinical trial or marketing authorisation. They may also arise from questions raised during a GCP inspection.

Inspection Procedures

Preparation of inspections: prior to conducting an inspection the inspector(s) should familiarise themselves with the organisation to be inspected.

This may include:

- Review of relevant parts of the investigational medicinal product dossier of one or more selected products to be examined during the inspection, including the History file
- For triggered inspections, a review of the questions raised by the Assessor or GCP Inspector (arising from a GCP inspection).

Review of documentation:

The system of documentation, based on the Product Specification Files, procedures and records covering the different production, QC and distribution operations should be checked by examining particular examples both during use and after compilation into complete batch records. Change control and the traceability of changes should be examined.

A general GMP-orientated inspection will normally, in order to assess compliance with the terms and conditions of the manufacturing authorisation, include examination of the documentation relating to:

- Product Specification Files
- Two-step batch release procedure and the role of the QP(s) including the assessment of products imported from third countries.

A product-related inspection will normally, in order to assess compliance with the terms and conditions of the investigational medicinal product dossier, include examination of the specific documentation relating to one or several completed batches of a specified product including:

- standard operating procedures (‘OP’s)
- the Product Specification File
Complaints and product recall

The system for recording and reviewing complaints, interactions with the clinical research personnel as well as the system for recalling batches of investigational medicinal products from within and outside the Member States should be examined during the inspection. The system for retrieving recall information on comparator products should also be included.

The complaints file should be examined. Defect Reports and recalls should be discussed.

Final Meeting

In case of serious deficiencies leading to possible serious risk for trial subjects, the inspector should take immediate action.
ANNEX 3

ON CONDUCT OF INSPECTIONS OF ACTIVE SUBSTANCE MANUFACTURERS

Introduction

The purpose of this document is to provide guidance on the conduct of inspection of a manufacturer of active substances as referred to in Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC in order to harmonise inspection procedures, frequency of inspections and follow-up procedures thus ensuring a consistent approach to assessment and decision-making by Competent Authorities.

Scope

This guideline applies to the inspection of active substance manufacturers as defined in Article 46 of Directive 2001/83/EC and Article 50 of Directive 2001/82/EC.

THIS ANNEX SHOULD BE READ IN CONJUNCTION WITH THE MAIN PROCEDURE. THE ANNEX PROVIDES ADDITIONAL INFORMATION ONLY

General Obligations

Member States

Member states should establish the legal and administrative framework within which inspections relating to Good Manufacturing Practice (GMP) inspections as applied to active substances operate.

Inspectors should be issued with an official means of identification, which includes reference to powers of entry, access to data and the collection of samples and documents for the purpose of inspection.

Member states should ensure that there are sufficient resources at all levels to effectively verify compliance with GMP for active substances and that inspectors are competent and trained in order to carry out their tasks.

Inspectorates should adopt quality systems to ensure consistency of approach to inspection and evaluation of findings. Within the quality system inspectorates should develop detailed procedures in line with this guideline to suit national requirements and practices but consistent with procedures agreed at Community level such as report formats for the exchange of information.

General Considerations on Inspections of Active Substances

The primary goal for the inspector should be to determine whether the various elements within the quality assurance system are effective and suitable for achieving compliance with GMP principles and pharmacopical requirements. In addition, when the inspection has been requested, for example, by the EDQM for the purpose of verifying whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, this must also be assessed.

Manufacture of active substances is defined in Article 46 of Directive 2001/83/EC and Article 50 of Directive 2001/82/EC as including both

- total and partial manufacture or import of an active substance used as a starting material
- and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of starting materials.
Inspections will therefore be performed of sites producing active substances and also those where active substances are being imported, repackaged or relabelled.

However the scope of the guidance given in Volume 4, EU Guidelines to Good manufacturing Practice, Medicinal Products for Human and Veterinary Use Part II, Basic Requirements for Active Substances used as Starting Materials should be noted as these apply to the manufacture of active substances for medicinal products for both human and veterinary use, but only apply to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC and interpreted in the GMP Guide including its Annex 1.

Whole blood and plasma are excluded, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood, however, active substances that are produced using blood or plasma as raw materials are included.

In the case of ectoparasiticides for veterinary use, other standards than the guidelines, that ensure that the material is of appropriate quality, may be used.

It should also be noted that Section 19 of the guidance covers the manufacture of new active substances used in the production of investigational medicinal products and although recommended its application in this case, is not required by Community legislation.

**Inspection Procedures**

**Preparation of inspections:** prior to conducting an inspection the inspector(s) should familiarise themselves with the organisation to be inspected.

This may include:

- Review of relevant parts of the active substance drug master file in addition to the items outlined in the main procedure or CTD for one or more selected products to be examined during the inspection.
- For triggered inspections, a review of the questions raised by the assessor or GMP inspector (arising from a GMP inspection of a manufacturing authorisation holder).
- Site Master File or other equivalent document.

**Review of documentation:**

An inspection will normally include examination of the documentation for one or several completed batches of a specified product relating to:

- job descriptions and training of staff
- standard operating procedures (SOPs)
- qualification reports
- validation reports
- manufacturing formulae, records and instructions
- reprocessing, reworking and solvent recovery SOPs
- specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products
- product quality review
• batch release
• complaints
• recalls

For sites that are importing, repackaging and relabeling active substances some of the above will not apply. Sites at which these activities are being performed should be assessed for compliance with the relevant sections of Part 2 of the GMP Guide including the requirements set out in chapter 17.

**Inspection Frequency**

Following Article 111 of Directive 2001/83/EC and Article 80 of 2001/82/EC a competent authorities should perform an inspections of active substance manufacturers whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of GMP. The European Directorate for the Quality of Medicines and HealthCare (EDQM) may request an inspection of the starting material manufacturer for the verification whether the data submitted in order to obtain a conformity certificate complies with the monographs of the European Pharmacopoeia. In line with these legal provisions the *Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials* details triggers for inspections. These principles do not imply a systematic approach for inspections of all active substance manufacturers.
Procedures Related to GMP Inspections

Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries

Table of contents:

- Verification of the GMP Compliance Status of Third Country Manufacturers of Medicinal and Investigational Medicinal Products
- Exchange of Information on Third Country Manufacturers
- Organisation and Records of Inspections and Composition of Inspection Teams
- Communication between the “Supervisory Authority” and Industry
- The “Supervisory Authorities”
- Re-inspection Frequency
- Disagreement between Member States on acceptability of Inspection Reports
- Annex

<table>
<thead>
<tr>
<th>Title</th>
<th>Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>December 2004</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>1 July 2005</td>
</tr>
<tr>
<td>Supersedes</td>
<td>Version published 1997</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>Reinforcing responsibilities for inspection and includes reference to investigational medicinal products. Provision is made for “Distant Assessment” in exceptional circumstances</td>
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<tr>
<td>Notes</td>
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</table>
Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries

1. Verification of the GMP Compliance Status of Third Country Manufacturers of Medicinal and Investigational Medicinal Products.

1.1 The Supervisory Member State for the manufacturing authorisation holder who is responsible for importation of a product should verify the GMP compliance status of any third country manufacturer(s) mentioned in an application in accordance with their own policies and procedures. This may be based on the following:

1.1.1 A report of an inspection for the product or product category concerned carried out by the Supervisory Member State, or

1.1.2 Information supplied by another EEA Competent Authority in accordance with the exchange of information procedure contained in the Compilation of Community Procedures,

Or

1.1.3 A report of an inspection for the product or product category concerned carried out by another EEA competent authority,

Or

1.1.4 Either an inspection report or a statement of GMP compliance obtained under an operational Mutual Recognition Agreement between the European Community and the Competent Authorities of the third country in which the manufacturer is located.

1.2 Where the Supervisory Member State is unable to verify the GMP status of any third country manufacturer(s) on the above basis it may request another EEA Competent Authority to carry out an inspection and to provide confirmation of the manufacturer’s GMP compliance status. For centralised products this arrangement should be subject to obtaining the written consent of any other Supervisory Member States involved.

1.3 The means of verification will normally be through inspection-based information as described above, however other information may be used as part of, or in exceptional cases, as the primary means for verification. For example:

1.3.1 Under the provisions of the existing MRAs, information from MRA partners is only accepted in connection with inspections performed in their own territories, however, the use of other information from MRA partners, PIC/S participating authorities and/or other authorities may nevertheless provide supporting evidence in the verification of the GMP status of a manufacturing site. The Supervisory Authority should perform a risk assessment on each occasion to determine an appropriate degree of evidence that a 3rd country manufacturer operates to an equivalent level of GMP.
1.3.2 Where an inspection has been performed by a Member State or MRA partner but
does not cover the dosage form in question. Compliance conclusions from
inspection reports relating to a different dosage form may, with justification, be
extended to other dose forms, if necessary requesting the report if it belongs to
another Member State authority. In addition the elements below should be
considered, together with, if considered necessary, elements of the distant
assessment approach described in section (c). Reports concerning non-sterile
dosage forms alone do not provide sufficient evidence to extend any GMP
conclusions to sterile products:

- Inspection reports of the importer. If necessary a special inspection may be
  needed of the importer to assess measures undertaken by the importer to verify
  GMP compliance at the exporting site for the dosage form in question, such as audit
  reports from the QP.

- A site master file for the manufacturing site. If necessary written questions
  arising from a review of this may need to be raised and the responses reviewed.

- The inspection history of the manufacturing site performed by other authorities.
The existence of warning letters or other regulatory action by third country
  authorities should be ascertained.

- The history of reported defects for batches of all products originating at the
  manufacturing site.

Subject to the information reviewed, it may be concluded not to conduct a pre-authorisation
inspection but verification in accordance with point 1.1 above should be sought within 3 years.

1.3.3 A similar approach can be taken where inspections cannot be carried out because
of unacceptable risks to EEA inspectors. The procedure for “distant assessment” is
limited to inspection in 3rd countries that present an enhanced physical threat to
the inspector (for political reasons, health reasons or others) and where the
enhanced level of instability is expected to be transient. The procedure should not
be used where the reporting authority has reason to believe that the instability
could directly affect the quality of the product(s) under consideration.

A distant assessment may be performed based on a documented interview with the
manufacturer that should be deep enough to evaluate the GMP compliance of the
relevant manufacturing site.

This documented interview (taking place in the inspecting authority’s country)
should be carried out with nominated staff possessing an appropriately high level of
knowledge of the process and facilities.

The table in the annex provides for two levels of assessment. A full assessment
where the site which has been inspected more than 5 years ago by an EEA
authority, and a reduced one for a site which has been inspected within 3 and 5
years ago by the same EEA Authority. If the last inspection was performed by
another authority, the full assessment should be applied.

A distant assessment should not be carried out where the manufacturing site has
never been inspected, by an EEA inspectorate, nor for a sterile manufacturing
process or any unusually complex non-sterile process, nor should it replace
inspection more than once.
1.4 Investigational Medicinal Products

For investigational medicinal products, inspections should be reserved for higher risk situations rather than being routinely employed. The risk assessments should take the elements described in 1. above into account along with the following:

- the dosage form,
- type of product (e.g. placebo, marketed comparator, new technology),
- numbers of subjects involved and their clinical disposition,
- duration of treatment,
- number of clinical trials sourcing from the same site
- whether the manufacturer is in possession of the equivalent of a valid manufacturing authorisation issued by its local regulatory authority and is subject to inspections,
- whether the analytical testing performed in the third country is subject to appropriate authorisation.

2. Exchange of Information on Third Country Manufacturers.

2.1 When exchanging information on third country manufacturing sites, the reporting authority should indicate whether the conclusions reached are derived from an inspection by an EEA inspectorate or MRA partner under the terms of an MRA, or whether alternative means were used such as those described in section 1.3.

2.2 On the basis of a "reasoned request" from the competent authorities of another Member State or from the EMEA the Supervisory Member State should provide a report of the most recent verification of the GMP status of a third country manufacturer for a particular product or product category.

2.3 Where the Member State requested to supply the information is unable to do so the requesting authorities may carry out a GMP inspection of the third country manufacturer, in which case they will provide the other authorities with shared supervisory responsibility with a copy of their inspection report or a statement of GMP compliance.

3. Organisation and Records of Inspections and Composition of Inspection Teams.

3.1 The EMEA will maintain a plan of third country inspections connected with centralised products and will make this available on a regular basis.

3.2 Through the database on GMP certificates to be established in accordance with Article 111.6 of Directive 2004/27 (Art. 80.6 of Directive 2004/28), the EMEA will maintain a record of all inspections that have been carried out by the competent authorities of the EU/EEA, which will be available to all member states.
3.3 The competent authorities planning inspections of manufacturers in third countries may invite the participation of the other Member States who have shared “Supervisory” responsibilities for the product(s). This should take into account planned applications for marketing authorisations, problems encountered with the products from the manufacturer, their workloads, their experience in the type of inspections required, language capability for the inspection and overall economics of travel etc.

4. Communication Between the “Supervisory Authority” and Industry

Member States should encourage potential applicants to make early contact with the inspectorate of the supervisory authority when planning a marketing authorisation submission or variation which includes a third country manufacturing site, in order to discuss the applicant’s knowledge of the GMP status of the site, its inspection history and inspection-readiness. Ideally this should be at least 3 months before submission and is particularly important for investigational medicinal products given the short timelines available to authorise trials.

5. The “Supervisory Authorities”

5.1 The “Supervisory Authorities” for a medicinal product and their responsibilities are defined for products for human use in Article 18 and 19 of Council Regulation (EC) No 726/2004 and for products for veterinary use in Articles 43 and 44 of the same Regulation. They are the Competent Authorities which have granted the manufacturing authorisation either for the manufacturing site if it is in the EU or for the importer if the product is manufactured in a third country.

6. Re-inspection Frequency

6.1 In general authorities with supervisory responsibility for a third country manufacturing site should ensure that it is re-inspected by an EEA authority or MRA partner authority, under the terms of an MRA, between every two to three years.

6.2 Where inspection reports and information exchange based on inspections conducted more than three years ago are available, as there is evidence of acceptable GMP standards, it should not be necessary to withhold any application or variation pending the results of a new inspection unless information is available from other sources suggesting that this status may have changed. Steps should nevertheless be taken to obtain an updated report.

6.3 Inspection reports, and information exchange based on inspections or distant assessments conducted more than five years ago, from whatever source, should not normally be taken into consideration.
7. Disagreement between Member States on acceptability of Inspection Reports

7.1 Where the Supervisory Member State and the competent authorities of another Member State are unable to agree on the acceptability of an inspection report for a manufacturer in a third country they should utilise the arrangements described for human products in Article 19 of Regulation (EC) 726/2004 or where appropriate the arbitration procedure provided by Article 29 of Directive 2001/83/EC and for veterinary products Article 44 of Regulation (EC) 726/2004 or where appropriate the arbitration procedure provided by Article 33 of Directive 2001/82/EC.
# 8. Annex

## SCHEME FOR DISTANT ASSESSMENT OF MANUFACTURING SITES

<table>
<thead>
<tr>
<th>Requirements / Rationale</th>
<th>Last EEA inspection more than 5 years ago</th>
<th>Last EEA inspection carried out between 3 and 5 years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation of GMP and Regulatory Enforcement system for the country</td>
<td>Complete presentation of the regulatory system and full copy of the local GMP guide</td>
<td>Brief presentation of changes being effected since the last inspection</td>
</tr>
<tr>
<td>Copy of the manufacturing authorisation granted by local authorities together with a certified translation</td>
<td>Complete set of copies of all original/modified manufacturing authorization</td>
<td>Copy of any new/modified manufacturing authorization granted since the last inspection</td>
</tr>
<tr>
<td>SMF (site master file) documentation similar to the PIC/S guideline</td>
<td>SMF completed/updated within 6 month from the assessment date And forecasted modifications</td>
<td>SMF updated with one year from the assessment date And forecasted modifications</td>
</tr>
<tr>
<td>Plans attached to SMF PI&amp;D attached to SMF</td>
<td>Coloured printouts of Water treatment, Air Handling PI &amp; Ds in A3 or A2 format</td>
<td>Coloured updated printouts may be acceptable in A3 or A2 format</td>
</tr>
<tr>
<td>List of all the products (medicinal or either) manufactured on site</td>
<td>The list should include proprietary names and INN</td>
<td>The list may include proprietary names and INN</td>
</tr>
<tr>
<td>Copy of the last inspection report with a certified translated copy if relevant GMP certificates coming from these inspections</td>
<td>Local authority report aged less than two years and, if available, copy of PIC/S or WHO or FDA report(s)</td>
<td>Last local authority report and last EU full report. PIC/S and WHO or FDA report(s) if aged less than 5 years</td>
</tr>
<tr>
<td>Photographic presentation of manufacturing site and utilities (outdoor/indoor)</td>
<td>External general view (aerial) Detailed rooms views of any step carried out (sample, weighing....)</td>
<td>Photographic presentation of any new room(s) of equipment not used at the time of inspection</td>
</tr>
<tr>
<td>Qualification Master Plan (premises &amp; equipment)</td>
<td>List of premises, equipment and utilities used in the manufacturing with their qualification status</td>
<td>List of all re-qualifications exercises carried out since the last inspection</td>
</tr>
<tr>
<td>Validation Master Plan (Manufacturing processes, cleaning, quality control)</td>
<td>List of processes used for the manufacturing / control of the product and their Val. status</td>
<td>List of all re-validations runs carried out since the last inspection</td>
</tr>
<tr>
<td>Full audit report of corporate / external audit dedicated to the product(s)</td>
<td>The report should include the product flow chart and should be one year old as a maximum</td>
<td>The report may be aged less than 5 years and accompanied with a recent follow-up internal report</td>
</tr>
<tr>
<td>Batch record(s) of the product(s) of interest</td>
<td>Last filled in batch record together the master batch record including the analytical part</td>
<td>Last filled in batch record including the analytical part</td>
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<td>Last EEA inspection carried out between 3 and 5 years ago</td>
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<td>All 00s results and investigations*</td>
<td>All 00s results and investigations*</td>
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<td>All process deviation reports (including reworked and reprocessed batches)*</td>
<td>All process deviation reports (including reworked and reprocessed batches)*</td>
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*data to be provided over a period of the last 3 years
Procedures Related to GMP Inspections

Guideline on Training and Qualifications of GMP Inspectors

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- Introduction
- Scope
- Background
- Qualification and Training
- Maintenance of Competence
- Harmonisation within EU

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<td>June 2008</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 31 December 2008</td>
</tr>
<tr>
<td>Supersedes</td>
<td>Version published October 2002</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>Updating</td>
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Guideline on Training and Qualifications of GMP Inspectors

1. Introduction

Taking into account its importance for the management of inspection services, this guideline establishes requirements concerning experience, training and qualifications of GMP inspectors.

Objectivity, professional integrity, competence in technical matters and inspection skills should be the main features of inspectors.

Inspectors should be very well trained in all the relevant topics concerning Quality Assurance management, manufacturing processes, control and distribution of medicinal products (including investigational medicinal product in the light of requirements of directive 2001/20/EC) and in the way of conducting an inspection (inspection methodology).

The guideline provides information on minimal requirements. Member States may decide to add supplementary national requirements.

2. Scope

This guideline applies to the training and qualifications required for an inspector who shall conduct an inspection to verify compliance with GMP for the competent authority of the Member State concerned. Inspections are carried out on behalf of the Community and the results shall be recognised by all the other Member States.

3. Background

3.1 General aspects

Member States should appoint inspectors to inspect the manufacturing sites according to Directive 2001/83/EC, Directive 2001/82/EC and Directive 2001/20/EC. There should be sufficient resources at all levels to meet, effectively and efficiently, the EU requirements of verifying compliance with GMP of medicinal products.

The inspectors shall be officials of, or appointed by, the competent authorities of the Member States in accordance with national regulations and follow the provisions for the national competent authority.

All inspectors should be competent to carry out their assigned duties and receive appropriate training. When needed, teams of inspectors may be nominated comprising inspectors with appropriate qualifications and experience to collectively fulfil the requirements necessary for conducting the inspection.

The inspectors should be made aware, of and maintain confidentiality whenever they gain access to confidential information as a result of GMP inspections according to applicable national laws, European requirements or international agreements.
There should be sufficient resource to ensure availability of competent inspectors to work according to contracts between EMEA and the competent authority in the case of inspections requested by the CHMP or CVMP.

The training needs of inspectors should regularly be assessed within the requirements of the applicable quality system of the Competent Authority/Inspectorate and appropriate actions taken by the competent authority to maintain and improve inspection skills.

Information on the relevant experience, training and qualifications of the individual inspector must be documented and maintained by the competent authority. These records should be kept up-to-date.

3.1 Personal qualities

The interpersonal skills of an inspector are important in helping to achieve the objectives of inspections.

During an inspection the inspector should help in creating an open atmosphere. Inspectors need to remain objective during the inspection and in this context should answer questions or provide clarification but avoid entering into the role of a consultant.

The inspector should have a high level of personal integrity, maturity, be open-minded, understanding of complexity, possess sound judgement, assertiveness, analytical skills and tenacity and have the ability to perceive situations in a realistic way.

The inspector should have demonstrated competence in clearly and fluently expressing concepts and ideas orally and in writing in their officially recognised language.

4. Qualification and Training

4.1 Qualification

Inspectors should preferably have the same level of qualification as the “Qualified Person” as defined in Art. 48 of Directive 2001/83/EC, in Art. 52 of the Directive 2001/82/EC and therefore be eligible as a Qualified Person.

The inspector should have knowledge of the national legislation as well as systems, both at national and at Community level, for applications for marketing and control of medicinal products.

4.2 Training

The inspectors should have undergone training to the extent necessary to ensure their competence in the skills required for planning, carrying out and reporting inspections.

The training and experience should be documented individually and evaluated within the requirements of the applicable quality system of the Competent Authority/Inspectorate.

4.2.1 Basic training

Moreover, in order to be appointed as GMP inspectors, the candidates should demonstrate their knowledge of the relevant matters in the pharmaceutical field, including:

- Community and national pharmaceutical legislation;
- Good Manufacturing Practice and Good Distribution Practice
- Principles of quality assurance and quality management systems (ISO 9000:2000);
- Technical aspects of pharmaceutical and API manufacturing (e.g. pharmaceutical technology, process and ventilation engineering, validation, computerized systems, analytical instrumentation, microbiology);
- Organization and quality systems of the Competent Authority/Inspectorate and training in working according to relevant national and Community SOPs and procedures related to inspections;
- Marketing and manufacturing authorisation systems and their relationship;
- Interrelation of licensing, inspection, sampling and analysis;
- Knowledge of MRA and other relevant Community arrangements;
- Structure and principles of operation of commercial organizations
- Inspection technique, acquired by attending relevant course(s) and or/by accompanying and/or guided by qualified GMP inspectors during inspection;
- Administration procedures required for managing an inspection, such as planning, organizing, communicating or providing feedback to the inspectee;
- Evaluation of findings and reporting;
- Pharmaceutical Development, Quality Risk Management and Pharmaceutical Quality System (incl. ICH Q8, Q9, Q10 as implemented in the relevant EU guidelines)
- International organisations their activities and documents (EDQM, ICH, PIC/S, WHO);

It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the Quality Assurance principles of Good Manufacturing Practice. An inspector should be open and able to assess whether alternative methods and procedures meet these principles taking into account the principles of Quality Risk Management.

4.2.2 Further training

After recruitment and in addition to their basic training, new inspectors should be trained by senior inspectors. The theory of inspection should be explained and the practice should be shown in the field, so that concrete examples of the meaning and of the goals of inspections are given and can be discussed. New inspectors should participate, but only as observers, in on the spot inspections carried out during their initial training.

Beside this and where needed, training courses in inspection techniques and communication, reporting, languages, legal matters and management should be organised by national inspectorates.

To be able to act as lead inspector in inspections requested by CHMP or CVMP and co-ordinated by EMEA and to participate in the ongoing co-operation and harmonisation of procedures within EU, the inspector should also be able to write and speak in English.
For participating to activities as such as Joint Audit Programme, Joint Reassessment Programme, European Benchmarking, adequate training should be organized at EU or international level as appropriate.

4.2.3. Continuous training

Considering the rapid implementation of new manufacturing technologies, the ever more frequent utilization of automatic and computerized systems both in production and quality control of medicinal products, inspectors should also receive continuous training.

This could be achieved through their participation in courses, seminars, scientific meetings and conferences organized either by the national inspectorates or by national or international scientific organizations.

When appropriate, joint inspections or training visits with other inspectors of the same Member State or of other Member States may be a useful training method.

Prior to assuming responsibility for performing GMP inspections the new inspector should have gained experience by participation as team member in inspections led by senior inspectors. Preferably, the inspector should start with national GMP inspections as a member of a team and then deal progressively with more complex GMP inspections to be able to act as a team leader and/or reporting inspector in international inspections. This should be recorded within the requirements of the applicable quality system of the Competent Authority/Inspectorate.

Ten days of training (e.g. courses, symposia, conferences, etc.) per year should be considered as a reasonable average.

4.3 Management capabilities

The inspectors should through suitable means demonstrate their knowledge and capability of using the necessary management skills required in the conduct of an inspection, i.e. planning, announcing, conducting and reporting an inspection.

4.4 Report writing

The inspector’s capacity to write inspection reports according to national and Community requirements should demonstrated and documented.

5. Maintenance of Competence

Inspectors should have their performance and qualifications periodically reviewed within the requirements of the applicable quality system of the Competent Authority/Inspectorate. Their competence should be maintained and updated by practical experience and by participating in courses, seminars, scientific meetings, conferences and through review of relevant publications. This should be documented and its effectiveness assessed to ensure that:

Knowledge of GMP, quality systems standards and requirements is current,

Knowledge of inspection procedures and methods is current,

Knowledge of quality assurance activities within the requirements of the applicable quality system of the Competent Authority/Inspectorate is current.
6. **Harmonisation within EU**

In order to promote international harmonisation in the interpretation of the principles of GMP and compliance, the Inspectorate’s management should facilitate training activities, including on the job training, at national and international levels.

Consultations with the staff of other GMP inspectorates and joint inspections or training visits are useful in this context and should be encouraged.

The management should also facilitate the exchange of information and practical experience gained by inspectors in the field of GMP, with inspectorates in other disciplines especially in those areas that are closely related e.g. laboratory facilities, computerised data recording and analyses and requirements in relation to medicinal products for investigational use.
Procedures Related to GMP Inspections

Guidance on the Occasions When It Is Appropriate for Competent Authorities to Conduct Inspections at the Premises of Manufacturers of Active Substances Used As Starting Materials

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- Purpose
- Scope
- Principle
- Examples of When Inspections May Be Appropriate
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<td>September 2005</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>1 October 2005</td>
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<td>Supersedes</td>
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Guidance on the Occasions When It Is Appropriate for Competent Authorities to Conduct Inspections at the Premises of Manufacturers of Active Substances Used As Starting Materials

1. Introduction

The legal basis for the regulation of medicinal products for Human and Veterinary use is determined by the Community Directives 2001/83/EC and 2001/82/EC, respectively. These Directives have been amended, correspondingly, by Directives 2004/27/EC and Directive 2004/28/EC to, inter alia, permit the inspection by Competent Authorities, under certain circumstances, of premises used to manufacture active substances. The relevant sections from the amended Directives 2001/83/EC and 2001/82/EC are set out in Annex 1.

2. Purpose

The purpose of this guidance is to encourage uniformity of approach regarding the decision making process as to when an inspection of a company which manufactures or distributes active substances may be appropriate. Repackaging or relabeling of active substances carried out by a distributor are considered as manufacturing activities.

3. Scope

The scope of this guidance covers the inspection activities of Member State Competent Authorities in relation to active substances that are used in the manufacture of human and/or veterinary medicinal products. This guidance applies to active substances manufactured inside and outside of the European Economic Area (EEA) (approximately 80% of active substances used in the manufacture of medicinal products within the EEA are manufactured outside of the EEA). The scope also includes activities carried out by distributors in line with the full definition of "manufacture of active substances used as starting materials" given in Annex 1 under Article 46(a) of Directive 2001/83/EC and Article 50(a) of Directive 2001/82/EC.

When a Mutual Recognition Agreement (MRA) is in place covering GMP for active substances, and where it is in accordance with the terms of the agreement, inspections performed by the MRA partner authority will take the place of inspections by the competent authorities of the EEA.

4. Principle

A Competent Authority must be able to satisfy itself that the manufacture and distribution of medicinal products has been carried out in accordance with the principles of good manufacturing practice and that the holders of manufacturing authorisations have only used active substances as starting materials which themselves have been manufactured and distributed in accordance with good manufacturing practice for active substances used as starting materials. Where it has grounds for suspecting non-compliance, the Competent Authority may carry out announced or unannounced inspections at the manufacturer or distributor of the active substance(s).
Article 46(f) of Directive 2001/83/EC and Article 50(f) of Directive 2001/82/EC oblige the holder of a manufacturing authorisation to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

When an application for a marketing authorisation, or variation to change or add a new active substance manufacturer, is submitted, the applicant will be required to include a declaration from the Qualified Person of the manufacturing authorisation holder that the active substance(s) concerned is/are manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

It is expected that the holder of the manufacturing authorisation will base such a declaration on carrying out, or having carried out on his behalf, an audit of the manufacturers/distributors of the active substances concerned. Examination, by inspectors, of the audit programmes used by authorisation holders for conducting regular audits (every 2 – 3 years), including review of audit reports, is one of the primary means by which Competent Authorities will determine if manufacturing authorisation holders are in compliance with the above articles.

Where the Competent Authority concludes that a manufacturing authorisation holder has not fulfilled its obligations under Article 46(f) of Directive 2001/83/EC and/or Article 50(f) of Directive 2001/82/EC regulatory action may be taken against the manufacturing authorisation holder and where necessary, appropriate action in connection with products on the market.

In compliance with Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC the Competent Authority may carry out an inspection of an active substance manufacturer in order to ensure that a manufacturing authorisation holder has fulfilled its obligations under Article 46(f) and/or Article 50(f) of the above mentioned Directives.

5. Examples of When Inspections May Be Appropriate

The following is a list of examples of when the inspection of premises used to manufacture a starting material, which is, in turn, used in the manufacture of a human or veterinary medicinal product, may be required. The legislation provides for unannounced inspections but this is not expected to become routine practice. Member States are expected to reserve unannounced inspections for occasions where such action is appropriate.

5.1 Directly linked to EU Legislation

5.1.1 When carried out by a Member State as part of the verification of the particulars submitted in support of an application for a marketing authorisation. This may apply in relation to marketing authorisation applications under national or mutual recognition or decentralised procedures and to application for variations to existing marketing authorisations (Article 19(1)/ Article 23(1))

5.1.2 When requested by another Member State where the requesting authority provides a written request detailing why an inspection is necessary. (Article 111(1)/Article 80 (1))

5.1.3 When requested by the European Commission where the Commission provides a written request detailing why an inspection is necessary (Article 111(1))/Article 80 (1)
5.1.4 When requested by the European Medicines Agency (EMEA) in relation to the assessment of a product under the centralised system or in connection with matters referred to it in accordance with Community legislation (Article 111(1)/Article 80 (1))

5.1.5 When requested by the Commission or the EMEA on behalf of the European Directorate for the Quality of Medicinal Products (EDQM) in order to verify if the data submitted in order to obtain a conformity certificate conforms with the monographs of the European Pharmacopoeia (Ph. Eur.) (Article 111 (1)/ Article 80 (1)) (Res AP/CSP (99)4)

5.1.6 When requested by the Commission or the EMEA on behalf of the EDQM where the latter suspects that there are grounds for suspending or withdrawing a conformity certificate (Certificate of Suitability) (Article 111(1)/Article 80(1) (Res AP/CSP (99)4).

5.1.7 Where the competent Authority considers that there are grounds for suspecting serious non-compliance with the principles of good manufacturing practice referred to in Article 47/Article 51 (Article 111(1)/ Article 80(1) – see also 2.3 below. This may also have regulatory consequences for relevant manufacturing authorisation holders.

5.1.8 Where there is disagreement between Member States on the conclusions from an inspection of a manufacturer of active substances to be used as starting materials for medicinal products (Article 122(3)/ Article 90(4)).

5.1.9 Where an uninvolved Member State is requested by the Commission to participate in a re-inspection in another Member State (Article 122(3)/ Article 90)

5.1.10 When requested by the manufacturer of an active substance located on the territory of a Member State of the EEA. Such an inspection may, for example, be for export purposes Article 111(1)/Article 80(1).

5.1.11 When requested by a manufacturer of an active substance, which is located in a non-European Economic Area (EEA) and non-Mutual Recognition Agreement (MRA) country. In such circumstances, at least one holder of a manufacturing authorisation supplied by the active substance manufacturer shall be located in the Member State of the competent authority which is requested to carry out the inspection (Article 111(1)/Article 80(1).

5.1.12 Where an active substance manufacturer supplies to a number of manufacturing authorisation holders in two or more Member States, the choice of competent authority to carry out the inspection is left to that active substance manufacturer.

5.2 Other examples

The following cases are examples for inspection triggers, where there is a suspicion of non-compliance with the GMP principles and guidelines in compliance with provisions of Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC. Examples 2.9 & 2.10 represent interfaces between manufacturing of the active substance and the finished medicinal product. It is therefore justified to include them in inspection schemes for medicinal products.
5.2.1 When analysis of a sample of an active substance used as a starting material carried out by, or on behalf of, the competent authority indicates significant non-compliance with the specification or suitability for use.

5.2.2 Following a report of a serious adverse reaction and/or recall of a medicinal product in which the quality of the active substance is implicated.

5.2.3 On receipt of information from another Competent Authority, based inside or outside the EEA, or other well-supported evidence, that activities at the premises are not compliant with the GMP principles. This may include premises located inside or outside the EEA. It may also include invocation of the safeguard clause contained in a MRA where the competent authority considers that it is imperative that an inspection of an active substance manufacturer located in the territory of an MRA partner be carried out.

5.2.4 Where there are suspicions regarding the authenticity of data, relating to an active substance. This would include data submitted in support of a marketing authorisation application, data provided on Certificates of Analysis or information on the identity of the original manufacturer of an active substance.

5.2.5 Where, during an inspection of a manufacturer of medicinal products, it is noted that there have been recurrent problems with the quality of individual batches of an active substance from a specific active substance manufacturer.

5.2.6 When recommended in an inspection report as a consequence of, or follow up to, observations from another inspection.

5.2.7 Where an inspection carried out on behalf of the EDQM reveals significant non-compliance with GMP principles, the competent authority may consider it appropriate to carry out a follow up inspection.

5.2.8 When a pharmacopoeial specification has been changed for significant safety reasons and there are grounds for suspecting that it has not been implemented by the active substance manufacturer.

5.2.9 When the active substance is a biological substance and the manufacturer is not subject to routine repeated inspections. Note: As the characterisation and quality of most biological substances is highly dependent on the production process, their manufacture is considered to be an integral part of the manufacturing process for the dosage form and should be subject to routine inspection.

5.2.10 When the active substance is presented as sterile and is to be incorporated aseptically during the manufacture of a medicinal product and the manufacturer is not subject to routine repeated inspections. Note: The sterilisation and subsequent aseptic handling of the active substance is considered to be part of the manufacturing process for the dosage form and should be subject to routine inspection. Steps preceding such sterilisation and aseptic handing, or when the substance is not intended to be incorporated aseptically fall under the guidance detailed in section 1 or the other parts of section 2.
5.2.11 As a measure to ensure that a manufacturing authorisation holder has fulfilled its obligations under Article 46(f) of Directive 2001/83/EC and/or Article 50(f) of Directive 2001/82/EC by virtue of Article 111 of Directive 2001/83/EC or Article 80 of Directive 2001/82/EC to ensure that the legal requirements governing medicinal products are complied with.

6. References


Procedures Related to GMP Inspections

The Issue and Update of GMP Certificates

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- Introduction
- Use of Certificates
- When GMP Certificates should be issued and EudraGMP database entry
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<td>By 30 September 2007</td>
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<td>GMP Certificates are issued, where appropriate, to manufacturers following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC and Art. 80(5) of Directive 2001/82/EC. They are also entered into the Community database (EudraGMP) as required in Arts 111(6) and 80(6) of the same directives</td>
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The Issue and Update of GMP Certificates

1. Introduction

Art. 111 (5) of Directive 2001/83/EC and Art. 80 (5) of Directive 2001/82/EC as amended, require a certificate of Good Manufacturing Practice to be issued to the manufacturer within 90 days of carrying out an inspection if the manufacturer complies with the principles and guidelines of GMP as provided for by Community law. The GMP certificates issued, or the information indicating that a manufacturer does not comply, shall be entered into the EudraGMP Community database.

The requirement specifically refers to inspections referred to in Art. 111 (1) of Directive 2001/83/EC and Art. 80 (1) of Directive 2001/82/EC, as amended. It includes therefore inspections of:

- Manufacturers, importers and contract laboratories according to national and centrally organised inspection programmes
- Active substance manufacturers, in particular where there are grounds for suspecting non-compliance, carried out in accordance with the Community Procedure entitled “Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials”, which includes requests by a manufacturer itself, member state, the Commission or EMEA. It also includes requests by EDQM on behalf of the Commission or EMEA as part of the certification procedure for monographs of the European Pharmacopoeia.
- Marketing authorisation holders in so far as compliance with Good Manufacturing Practice is concerned
- Manufacturers located in third countries,

The requirement applies regardless as to whether the inspections are unannounced, routine or requested by a Member State, the European Commission, European Medicines Agency, EDQM or manufacturer itself.

In addition where appropriate, and where the national competent authority chooses to do so, GMP certificates may be issued following inspection of manufacturers of investigational medicinal products for human use. In any case entry into EudraGMP database will be made to fulfil Art. 11(1) f of Directive 2001/20/EC.

This document is intended to give interpretation on aspects of responsibilities of the issue, renewal and update of GMP certificates.
2. Use of Certificates

GMP certificates are for the purpose of confirming to a manufacturer (whether for active substances or medicinal products) the overall conclusion of an inspection with respect to compliance with GMP. In some cases, particularly outside of the EEA, they may be used by applicants to support regulatory submissions. Within the EEA they do not replace confirmation of the holding of a manufacturing authorisation. The GMP status of third country manufacturing sites for medicinal products and active substances may be confirmed using the EudraGMP database or until this is fully operational, confirmed using the Community procedure for the exchange of information.

For active substances, the supporting document in regulatory submissions is the declaration by the Qualified Person of the manufacturing authorisation holder that uses the active substance as a starting material.

GMP certificates issued by EEA authorities are recognised within the framework of WHO and to fulfil obligations under the Mutual Recognition Agreements were agreed.

3. When GMP Certificates Should Be Issued and EudraGMP Database Entry

3.1 Responsibility for issue of GMP Certificates

For medicinal products responsibility for issuing GMP certificates and placing entries into EudraGMP rests with the supervisory authority, including those certificates issued following inspections performed at the request of the Commission, EMEA, EDQM, Member State or an active substance manufacturer as well as inspections performed by another member state on behalf of the supervisory authority. If there is more than one supervisory authority for third country manufacturers then these authorities should agree on who will take on this responsibility but normally one of the supervisory authorities will lead the inspection and this one should take responsibility.

In the case of an inspection of an active substance manufacturer, as the concept of supervisory authority does not apply, responsibility for the GMP certificate and EudraGMP entry rests with the authority that carries out or leads the inspection.

Following each relevant inspection, a report in accordance with the Community format should be produced by the responsible inspector or inspection team, which should contain a clear statement as to whether or not the manufacturer complies with the principles and guidelines of GMP as provided for in Community legislation. Where this is the case, within 90 days of the last day of the inspection concerned, the supervisory authority should issue a GMP certificate in accordance with the Community format to the manufacturer that underwent the inspection. In the case of non-compliance see the relevant Community procedure.

Each certificate should include a reference that enables traceability within the inspectorate that issued it so that the inspectorate can respond promptly to enquiries regarding authenticity.

Duplicates of valid GMP certificates may be issued in response to a request from the manufacturer, or MRA partner authority in accordance with the terms of the agreement.
3.2 Circumstances where the issue of a certificate to a manufacturer may not be applicable (other than in cases of failure to comply with GMP).

If the aim of any particular visit to a site is not primarily to assess compliance with GMP and the issue of a certificate is therefore not foreseen, then this should be made clear to the concerned manufacturer at the outset.

It may not be appropriate to issue a GMP certificate following an inspection in response to an application for, or variation to a manufacturing authorisation, even if the outcome of the inspection is positive with respect to the application, particularly where approval is based upon plans and commitments rather than a direct inspection of facilities and operations.

Normally, an inspection is conducted in a single visit over a consecutive period of days but it may be split into a number of separate visits. Provided the subsequent visits occur within a reasonable period of time of the first visit, as decided by national procedures, the individual visits may collectively be considered as one inspection for which a single certificate will be issued within 90 days of the last day of the last visit. The manufacturer should be informed of this beforehand.

A GMP certificate is not issued to a third country manufacturer when the GMP status has been verified using the distant assessment procedure described in the Community procedure on co-coordinating the verification of the GMP status of manufacturers in third countries. A EudraGMP database entry is nevertheless made (see section 3.6).

Depending on national procedures, GMP certificates need not be issued to manufacturers of investigational medicinal products. Nevertheless EudraGMP entry will be required (see section 3.7).

3.3 Scope of individual certificates

The certificate should include all operations deemed to be GMP compliant as a result of the inspection. For large sites in the EEA this may not necessarily include all authorised operations as several inspections may be needed to assess all the authorised operations over a period of time as agreed in Community procedures.

Inspections performed at third country manufacturers are often particularly restricted in scope and provision is made for this in part 2 of the certificate format. For ease of database entry and to reduce the use of free text, the EudraGMP database contains standard phrases to cover the most common situations.

3.4 Responsibility for EudraGMP database entry

The supervisory authority may enter the details of the certificate into the EudraGMP before or at the time the certificate itself is issued to the manufacturer, or as soon as possible thereafter. Database entries will have a status of draft, current or withdrawn.

3.5 EudraGMP entry for GMP Certificates issued by MRA Partners

The information from GMP certificates issued by MRA partner authorities is, on the first occasion, input into EudraGMP by the requesting authority in the EEA. Once the necessary agreements are in place it is suggested that subsequent certificates for the same site are input directly by the MRA partner. In the absence of such an agreement subsequent certificates will continue to be input by the requesting authority in the EEA.
3.6 Distant assessment

When the GMP status of a manufacturer located in a third country has been verified using the distant assessment procedure described in the Community procedure on co-coordinating the verification of the GMP status of manufacturers in third countries, no certificate should be issued to the manufacturer in question but an entry in the EudraGMP database should nevertheless be made by the supervisory authority indicating in the relevant field that the distant assessment procedure was followed.

3.7 Investigational Medicinal Products for Human Use (IMPs)

Directive 2001/83/EC does not make reference to the issue of GMP certificates following an inspection of a manufacturer of IMPs, however Member States may choose to do so. In order to facilitate the exchange of information on clinical trials Art. 11 of Directive 2001/20/EC requires a reference to inspections to be included in a European database and it has been agreed that the appropriate database is EudraGMP database for GMP inspections of manufacturers of IMPs. Therefore an entry should be made whether or not a certificate is issued to the manufacturer in question.

4. Non-compliance With GMP

A separate Community procedure deals with the handling of non-compliance.

5. Renewal and Update of GMP Certificates

5.1 A certificate itself is not renewed, as it is a declaration of the status of GMP compliance at a particular point in time connected with a satisfactory inspection outcome. A new certificate will be issued following the next inspection, if appropriate. Entries in EudraGMP however require a different approach.

EudraGMP requires the Member State inputting new information to decide whether the new certificate replaces an existing entry for the site in question, in which case they must take action to withdraw the superseded information, or, whether the information is in addition to the existing information, in which case the information being supplemented should remain in the database. In the case of third country manufacturers with more than one supervisory authority it is possible that a different authority carries out the subsequent inspection but it is not possible for an authority to withdraw a database entry made by another authority. Therefore both authorities have to work together to maintain the database in order that superseded information is withdrawn by the supervisory authority that originally input it.

However, sometimes it will be necessary to retain some of the existing information if it is not superseded following a new inspection. This would happen, for example, when the most recent inspection does not cover everything covered by the previous inspection. In this case the following action is appropriate:

- Withdraw the existing certificate (or have the original issuing authority withdraw it) and re-issue it having removed the superseded information but retaining the original date of inspection.
- Issue a further new certificate with new information and the most recent inspection date.
5.2 Administrative updates and re-issue

An updated certificate may be issued to a manufacturer and input into EudraGMP by the authority that issued the last certificate at the request of a manufacturer when administrative changes occur that affect the details appearing on the certificate and where the supervisory authority agrees that a re-inspection is not required. An example would be a change in the name of the manufacturer. These new certificates will supersede the existing certificate but will maintain the original date of inspection, as an inspection will not have been carried out.

6. Closure of Manufacturing Site

Member states should take steps to ensure that when a site under its supervision ceases to operate, any GMP certificate is withdrawn from the Community database along with any manufacturing authorisation and non-compliance information.
Appendix

Site visit

Last visit of the inspection?

Yes

Is the site seriously non-compliant and urgent action required?

Yes

The next step occurs when the inspection conclusion has been confirmed or 90 days have elapsed since the last day of the inspection

Yes

Is there some outstanding area of non-compliance?

No

Yes

Refer to relevant community procedure

No

Yes

Defer conclusion until inspection can be performed

Some or all operations are GMP compliant

GMP certificate received from MRA partner

Distant assessment performed

Database entry

GMP certificate received from MRA partner

End

End

No

Yes

No

Yes

GMP certificate received from MRA partner

Distant assessment or certificate from partner?
Procedures Related to GMP Inspections

A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers

Table of contents:

- Introduction
- Purpose
- Scope
- Procedure

<table>
<thead>
<tr>
<th>Title</th>
<th>A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>November 2007</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>April 2008</td>
</tr>
<tr>
<td>Supersedes</td>
<td>N/A</td>
</tr>
<tr>
<td>Reason for revision</td>
<td></td>
</tr>
</tbody>
</table>

Notes

This procedure is optional.

Section 4.4 includes proposals by ICH Q9 drafting group. Member States may use other descriptors for assigning the compliance factor referred to in section 4.4.4. Further categories may be defined as appropriate. The factors identified in section 4.4.3 may affect the compliance factor determined in section 4.4.4.
A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers

1. Introduction

1.1 According to directive 2001/83/EC, 2001/82/EC and 2001/20/EC, respectively, the Competent Authority shall ensure, by means of repeated inspections, and if necessary unannounced inspections, that the legal requirements governing medicinal products are complied with. The Competent Authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice.

1.2 A risk based approach to inspection planning will enable the frequency, depth and breadth of inspections to be determined accordingly. This will allow flexible and effective administration, whilst maintaining a high level of patient safety.

1.3 Competent Authorities of the Member States need to develop a systematic and risk-based approach to make the best use of their surveillance and enforcement resources while maximizing the impact of those resources on the public health.

1.4 Each Competent Authority should have a written procedure that covers the preparation, realization and supervision of an annual inspection programme. This programme should ensure that the extent and frequency of inspections can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner.

2. Purpose

2.1 This document outlines recommendations for a risk based planning system according to which sites that fall under regulatory supervision are subject to inspection.

2.2 It is intended that each GMP Pharmaceutical Inspectorate uses the document as the basis for developing and implementing its own annual inspection programme.

2.3 Competent authorities are free to develop and/or use the most appropriate risk tool to achieve this aim based on the elements outlined in this document.

3. Scope

3.1 This procedure covers the field of inspection of manufacturers of medicinal products, investigational medicinal products, biological substances and sterilisation of active substances.

3.2 This procedure covers both human and veterinary medicinal products.
4. Procedure

4.1 Principle

Planning and scheduling of inspections is realized as follows:

- compile all relevant sites/facilities in a list
- establish risk ranking (based on product risk and compliance factor) for each site
- establish the necessary expenditure of inspection time for each site
- establish the inspection frequency
- prioritize inspections by calculating individual inspection dates per site
- establish risk ranking

4.2 Inspections-site list

All sites/facilities that are subject to inspection are to be listed in an appropriate up to date list. This list could include the following information:

<table>
<thead>
<tr>
<th>List of sites subject to inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Name and address of inspectorate</td>
</tr>
<tr>
<td>• Name of the competent inspector</td>
</tr>
<tr>
<td>• Name and address of each site</td>
</tr>
<tr>
<td>• Dosage forms manufactured per site</td>
</tr>
<tr>
<td>• Number of deficiencies categorised according to the Definition of Significant Deficiencies laid down in the GMP Inspection Report - Community format</td>
</tr>
<tr>
<td>• Date of the last inspection per site</td>
</tr>
<tr>
<td>• Number of inspection days required per site</td>
</tr>
<tr>
<td>• Inspection frequency per site</td>
</tr>
<tr>
<td>• Date of the next inspection</td>
</tr>
</tbody>
</table>

4.3 Expenditure of time

The following table presents guidance values for the required inspection time per type of site. The type of manufacturing site is classified by the relevant dosage form and the manufacturing process, respectively.

The risk ranking of the type of manufacturing site is based on the assessment of the risk severity, probability of occurrence and probability of detection with respect to product quality defects and process safety issues. This risk ranking assumes that critical processes and products (e.g. sterile products) would have a higher public health consequence than less critical products and processes; hence these products are given a higher weight.
### Classification of manufacturing or importation sites according to the type of product/process

<table>
<thead>
<tr>
<th>1.1</th>
<th>Sterile Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1</strong> Aseptically prepared (list of dosage forms)</td>
<td><strong>≥ 10</strong></td>
</tr>
<tr>
<td>1.1.1.1 Large volume liquids</td>
<td></td>
</tr>
<tr>
<td>1.1.1.2 Lyophilisates</td>
<td></td>
</tr>
<tr>
<td>1.1.1.3 Semi-solids</td>
<td></td>
</tr>
<tr>
<td>1.1.1.4 Small volume liquids</td>
<td></td>
</tr>
<tr>
<td>1.1.1.5 Solids and implants</td>
<td></td>
</tr>
<tr>
<td><strong>1.1.2</strong> Terminally sterilised (list of dosage forms)</td>
<td><strong>≥ 8</strong></td>
</tr>
<tr>
<td>1.1.2.1 Large volume liquids</td>
<td></td>
</tr>
<tr>
<td>1.1.2.2 Semi-solids</td>
<td></td>
</tr>
<tr>
<td>1.1.2.3 Small volume liquids</td>
<td></td>
</tr>
<tr>
<td>1.1.2.4 Solids and implants</td>
<td></td>
</tr>
<tr>
<td><strong>1.1.3</strong> Batch certification</td>
<td><strong>≥ 1</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.2</th>
<th>Non-sterile products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1</strong> Non-sterile products (list of dosage forms)</td>
<td><strong>≥ 4</strong></td>
</tr>
<tr>
<td>1.2.1.1 Capsules, hard shell</td>
<td></td>
</tr>
<tr>
<td>1.2.1.2 Capsules, soft shell</td>
<td></td>
</tr>
<tr>
<td>1.2.1.3 Chewing gums</td>
<td></td>
</tr>
<tr>
<td>1.2.1.4 Impregnated matrices</td>
<td></td>
</tr>
<tr>
<td>1.2.1.5 Liquids for external use</td>
<td></td>
</tr>
<tr>
<td>1.2.1.6 Liquids for internal use</td>
<td></td>
</tr>
<tr>
<td>1.2.1.7 Medicinal gases</td>
<td></td>
</tr>
<tr>
<td>1.2.1.8 Other solid dosage forms</td>
<td></td>
</tr>
<tr>
<td>1.2.1.9 Pressurised preparations</td>
<td></td>
</tr>
<tr>
<td>1.2.1.10 Radionuclide generators</td>
<td></td>
</tr>
<tr>
<td>1.2.1.11 Semi-solids</td>
<td></td>
</tr>
<tr>
<td>1.2.1.12 Suppositories</td>
<td></td>
</tr>
<tr>
<td>1.2.1.13 Tablets</td>
<td></td>
</tr>
<tr>
<td>1.2.1.14 Transdermal patches</td>
<td></td>
</tr>
<tr>
<td>1.2.1.15 Intraruminal devices</td>
<td></td>
</tr>
<tr>
<td>1.2.1.16 Veterinary premixes</td>
<td></td>
</tr>
<tr>
<td><strong>1.2.2</strong> Batch certification</td>
<td><strong>≥ 1</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.3</th>
<th>Biological medicinal products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.3.1</strong> Biological medicinal products</td>
<td><strong>≥ 7</strong></td>
</tr>
<tr>
<td>1.3.1.1 Blood products</td>
<td></td>
</tr>
<tr>
<td>1.3.1.2 Immunological products</td>
<td></td>
</tr>
<tr>
<td>1.3.1.3 Cell therapy products</td>
<td></td>
</tr>
<tr>
<td>1.3.1.4 Gene therapy products</td>
<td></td>
</tr>
<tr>
<td>1.3.1.5 Biotechnology products</td>
<td></td>
</tr>
<tr>
<td>1.3.1.6 Human or animal extracted products</td>
<td></td>
</tr>
<tr>
<td><strong>1.3.2</strong> Batch certification only (list of product types)</td>
<td><strong>≥ 1</strong></td>
</tr>
<tr>
<td>1.3.2.1 Blood products</td>
<td></td>
</tr>
<tr>
<td>1.3.2.2 Immunological products</td>
<td></td>
</tr>
<tr>
<td>1.3.2.3 Cell therapy products</td>
<td></td>
</tr>
<tr>
<td>1.3.2.4 Gene therapy products</td>
<td></td>
</tr>
<tr>
<td>1.3.2.5 Biotechnology products</td>
<td></td>
</tr>
<tr>
<td>1.3.2.6 Human or animal extracted products</td>
<td></td>
</tr>
</tbody>
</table>
### 1.4 Other products or manufacturing activity

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 Manufacture of:</td>
<td></td>
</tr>
<tr>
<td>1.4.1.1 Herbal products</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>1.4.1.2 Homoeopathic products</td>
<td></td>
</tr>
<tr>
<td>1.4.1.3 Biological active starting materials</td>
<td></td>
</tr>
<tr>
<td>1.4.2 Sterilisation of active substances/excipients/finished product:</td>
<td>&gt;2</td>
</tr>
<tr>
<td>1.4.2.1 Filtration</td>
<td></td>
</tr>
<tr>
<td>1.4.2.2 Dry heat</td>
<td></td>
</tr>
<tr>
<td>1.4.2.3 Moist heat</td>
<td></td>
</tr>
<tr>
<td>1.4.2.4 Chemical</td>
<td></td>
</tr>
<tr>
<td>1.4.2.5 Gamma irradiation</td>
<td></td>
</tr>
<tr>
<td>1.4.2.6 Electron beam</td>
<td></td>
</tr>
</tbody>
</table>

### 1.5 Packaging

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5.1 Primary packing</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>1.5.1.1 Capsules, hard shell</td>
<td></td>
</tr>
<tr>
<td>1.5.1.2 Capsules, soft shell</td>
<td></td>
</tr>
<tr>
<td>1.5.1.3 Chewing gums</td>
<td></td>
</tr>
<tr>
<td>1.5.1.4 Impregnated matrices</td>
<td></td>
</tr>
<tr>
<td>1.5.1.5 Liquids for external use</td>
<td></td>
</tr>
<tr>
<td>1.5.1.6 Liquids for internal use</td>
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<tr>
<td>1.5.1.7 Medicinal gases</td>
<td></td>
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<td>1.5.1.8 Other solid dosage forms</td>
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<tr>
<td>1.5.1.9 Pressurised preparations</td>
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</tr>
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<td>1.5.1.10 Radionuclide generators</td>
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<td>1.5.1.11 Semi-solids</td>
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<td>1.5.1.12 Suppositories</td>
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<td>1.5.1.13 Tablets</td>
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<td>1.5.1.14 Transdermal patches</td>
<td></td>
</tr>
<tr>
<td>1.5.1.15 Intraruminal devices</td>
<td></td>
</tr>
<tr>
<td>1.5.1.16 Veterinary premixes</td>
<td></td>
</tr>
<tr>
<td>1.5.2 Secondary packing</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>

### 1.6 Quality control testing

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6.1 Microbiological: sterility</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>1.6.2 Microbiological: non-sterility</td>
<td></td>
</tr>
<tr>
<td>1.6.3 Chemical/Physical</td>
<td></td>
</tr>
<tr>
<td>1.6.4 Biological</td>
<td></td>
</tr>
</tbody>
</table>

The overall inspection days are guidance values and include the necessary time for preparation and report of the inspection and represent the total personnel expenditure (e.g. 10 overall inspection days equals in 2 inspectors inspecting for 5 days or 4 inspectors inspecting for 2½ days; preparation and report time included).
Depending on the:

- type of inspection (full vs. part inspection),
- complexity of the site (size, variety of facilities),
- complexity of the manufacturing process (type and sequence of operations, process controls applied),
- the complexity of the product and its therapeutic significance and
- patient exposure

the required inspection time may be adjusted accordingly.

4.4 Frequency of inspections

4.4.1 Large companies may be inspected department by department, a full general GMP inspection being completed at least every five years. Generally the interval between inspections should not exceed 3 years as lack of continuity may give rise to lower awareness of current GMP or allow significant deficiencies to develop. The necessity to carry out immediate inspections e.g. due to product quality defects or significant changes of building, equipment or processes is not affected.

4.4.2 Companies representing a low risk and meeting the expectation of GMP at a high level do not have to be inspected as often as the ones that manufacture products or perform activities representing great risk and operate with great deficiencies. It should be stressed that the activities of the individual company (e.g. products and dosage forms manufactured, units and substances handled and personnel, premises and equipment involved in the manufacture) and its past record of GMP compliance should be taken into consideration when planning the frequency and duration of inspection. Accordingly a review of the observations arising from the last inspection including all deficiencies will form a major precondition for the subsequent decision on an adequate inspection frequency.

4.4.3 To define the frequency of inspections the competent authority should take into account, amongst others, factors such as:

- The agency’s knowledge of the company (overall compliance status and history of the company or facility);
- Results of product testing by OMCL’s;
- Number and significance of quality defects (e.g. recall);
- Results of previous inspections;
- Compliance information from agencies/bodies outside the EU;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches).

4.4.4 Generally the frequency of inspections can be categorized as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Inspection interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance Factor I Poor Compliance</td>
<td>The last inspection revealed critical and/or more than/equal to six (≥ 6) major deficiencies</td>
<td>1 year</td>
</tr>
<tr>
<td>Compliance Factor II Acceptable Compliance</td>
<td>The last two inspections revealed no critical and less than six (&lt; 6) major deficiencies</td>
<td>2 years</td>
</tr>
<tr>
<td>Compliance Factor III Good Compliance</td>
<td>The last two inspections revealed no critical and major deficiencies</td>
<td>3 years</td>
</tr>
</tbody>
</table>

* Deficiencies are categorized according to the Definition of Significant Deficiencies laid down in the GMP Inspection report - Community format.
4.5 Calculation of the next inspection date
The calculation of the next inspection date results from the last inspection date and the inspectorate's risk assessment process.

4.6 Responsibilities and supervision
The responsibility for the compilation and supervision of an annual inspection programme should be defined within the GMP Pharmaceutical Inspectorate. A periodical review of the inspection programme should ensure that serious deviations from the time plan are noticed and corrective actions taken as necessary.
Procedures Related to GMP Inspections

Procedure for Dealing with Serious GMP Non-compliance or Voiding/Suspension of CEPS Thus Requiring Co-ordinated Administrative Action

Table of contents:

- Summary
- Definitions
- Principles
- Scope
- Responsibilities
- Types and consequences of administrative action
- Communication
- Procedure post-communication: Serious GMP Non-compliance
- Legal References
- Annex 1: Action of Authority Discovering GMP Non-Compliance
- Annex 2: Action by Authorities following Receipt of Information of GMP Non-Compliance
Procedure for Dealing with Serious GMP Non-compliance or Voiding/Suspension of CEPS Thus Requiring Co-ordinated Administrative Action

1. Summary

A consolidated procedure for dealing with all circumstances of serious GMP non-compliance, whether found at a manufacturing or import authorisation holder, third country manufacturer or active substance manufacturer is necessary to ensure a coordinated approach to potential risks to public/animal health.

This document replaces Appendix 3 of the Community procedure for the exchange of Information on Manufacturers and Manufacturing or Wholesale Distribution Authorisations between Competent Authorities in the European Economic Area. The appendix of which deals with serious GMP non-compliance found at a third country manufacturing site where co-ordinated administrative action is necessary.

Suspension or voiding of a Certificate of the European Pharmacopoeia (CEP) may be a recommended action following an inspection of an active substance manufacturer but this procedure additionally addresses action to be taken in the event of notification by EDQM that a CEP has been voided or suspended for reasons other than serious GMP non-compliance as the actions and consequences are similar.

The reporting inspectorate should enter the information on serious GMP non-compliance in EudraGMP, as referred in Article 111(6) (80(7)) of Directive 2001/83(2)/EC.

The procedure requires the inspectorate discovering serious GMP non-compliance to recommend appropriate action, involving other authorities that share supervisory responsibility in developing those recommendations, and to communicate the recommendations to all other authorities in the Community. Communication with authorities of those countries, with which the Community has made appropriate arrangements on GMP (e.g. MRA) may also be necessary.

Provision is made in the procedure for a teleconference to give authorities receiving notification of serious GMP non-compliance an opportunity to seek clarifications and to confirm the appropriateness of the recommended actions before they are implemented at Community level.

National competent authorities must take into account the information on serious GMP non-compliance received and should follow the actions recommended, where the procedure requires it to do so, unless it can justify alternative action based on specific national considerations and where those alternative actions have no impact on other Member States.

With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for mutual recognition/de-centralised products. The European Medicines Agency co-ordinates action for centrally authorised products. Each national competent authority takes responsibility for marketing authorisations that exist purely at national level.
2. Definitions

2.1 For the purposes of this procedure, serious GMP non-compliance is non-compliance with GMP that in the opinion of the reporting inspectorate is of such a nature that administrative action is necessary to remove a potential risk to public/animal health.

2.2 For the purposes of this procedure, administrative action is one of the actions described in section 6.

3. Principles

3.1 A GMP inspection report should make a clear conclusion as to whether a manufacturer or importer generally complies or not with the principles and guidelines of GMP as defined in Directive 93/2004/EC and/or 91/412/EEC and as interpreted in Guidelines on GMP published by the European Commission in Eudralex Volume 4. It is understood that a company can be considered to be in general compliance even if there is degree of non-compliance, which the inspector is satisfied can be resolved without administrative action being taken.

3.2 Action following the discovery of any non-compliance should be commensurate with the level of risk posed by the non-compliance. Serious non-compliance by definition requires administrative action to be taken.

3.3 All inspections carried out by the inspection services of any Member States are performed on behalf of the entire Community. The discovery of serious GMP non-compliance may have implications not only for the Member State carrying out the inspection but also other, possibly all, Member States. Therefore a mechanism that ensures consistent, co-ordinated action throughout the Community is required.

3.4 Although Member States may make a reasoned request to another Member State to receive an inspection report, the authority that carries out the inspection, with first-hand information is best placed to assess the potential impact of, and to manage the risk posed by, the level of GMP non-compliance discovered.

3.5 Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Community action in connection with a marketing authorisation, or a rapid alert is not considered, on balance, to be in the interest of public/animal health in any particular Member State, that Member State may, in accordance with Community legislation, decide to take alternative action to that proposed by the Member State revealing the serious GMP non-compliance.

3.6 With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for mutual recognition/de-centralised products. The European Medicines Agency co-ordinates action for centrally authorised products. Each national competent authority takes responsibility for marketing authorisations that exist purely at national level.

3.8 Unnecessary communication of non-compliance should be avoided in order to make efficient use of the Community alert mechanisms.

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1 This includes inspections requested by the European Commission, the European Medicines Agency and EDQM but excludes those performed under contract to WHO. Until further notice serious non-compliance discovered during an inspection on behalf of WHO is not subject to this procedure.
4. Scope

4.1 Most GMP inspections reveal a degree of non-compliance and even if failures to comply are cited as being "major", or occasionally, "critical", matters can usually reach a satisfactory conclusion, sometimes involving follow-up inspections, without administrative action being taken. This procedure applies only when the level of non-compliance is such that the inspector concerned recommends that administrative action is taken to remove a potential risk to public/animal health and that recommendation is ratified in accordance with internal national procedures. Procedures should require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

4.2 This procedure applies to all GMP inspections where serious GMP non-compliance is discovered whether in the territory of the Supervisory Authority or, in third countries, including inspections requested by the manufacturer, importer, European Commission, European Medicines Agency or EDQM. It applies to inspections of active substance manufacturers, manufacturers or importers of medicinal products, manufacturers or importers of investigational medicinal products as well as quality control laboratories. It applies to inspections in third countries covered under the distant assessment procedure.

4.3 In order to avoid unnecessary use of Community alert mechanisms, communication of serious GMP non-compliance in accordance with this procedure should not be initiated when the information and action is of no interest to any other Member State. Examples are given in 6.1.2

4.4 All serious GMP non-compliance relating to active substance manufacturers and all types of manufacturers located in third countries must be communicated even if it is known that no other Member State has an interest at the time as it may be important for all Member States to have the information available in the future.

4.5 The discovery of serious GMP non-compliance at an active substance manufacturer associated with a CEP and inspected at the request of EDQM may lead to action by EDQM in connection with the CEP, such as suspension or voiding. This procedure must nevertheless still be invoked in order to ensure coordinated, harmonised action regarding the serious GMP non-compliance itself.

4.6 The procedure also deals with cases where a CEP is declared void by EDQM for reasons unrelated to an inspection outcome as consequential action may be needed, which must be properly implemented and coordinated.

5. Responsibilities

5.1 Following a GMP inspection, the inspection report must conclude whether the inspected company complies with the principles and guidelines of GMP or not. If the conclusion is that the inspected company does not comply, then the inspector concerned should recommend what risk-mitigating action is necessary such as administrative action, including whether a rapid alert is necessary for products/batches released onto the market and/or whether a prohibition of supply should be enforced.

5.2 With regard to inspections relating to medicinal products and investigational medicinal products, if the authority performing the inspection is not the Supervisory Authority it should involve the Supervisory Authority before issuing any non-compliance report so that any proposed regulatory action can be initially agreed.
5.3 Each national competent authority should have an internal national procedure to review inspection reports from its own inspectors which recommend administrative action in order to decide whether to support the inspectors recommended action or whether alternative action is more appropriate. This decision should be reached, and if administrative action is supported, communicated to other competent authorities in accordance with this procedure, within a timeframe appropriate to the potential threat to public health.

5.4 The Supervisory Authority is responsible for taking action against manufacturing or import authorisation holders under its supervision and/or disciplinary action against QPs connected with manufacturing authorisations under its supervision.

5.5 With regard to marketing authorisations, any recommendations made by the authority reporting the serious GMP non-compliance must take account of the interests of the Community as a whole, regardless as to any specific national considerations as referred to in the principle 3.5 above.

5.6 With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for mutual recognition/de-centralised products. The European Medicines Agency co-ordinates action for centrally authorised products. Each national competent authority takes responsibility for marketing authorisations that exist purely at national level.

5.7 Prohibition of supply as a result of GMP non-compliance is action in connection with the marketing authorisation and responsibility should be taken as described in 5.6.

5.8 In the context of an MRA, partners are obliged to notify recipients of GMP certificates exchanged when those certificates are withdrawn due to GMP non-compliance. Since manufacturers themselves may also request GMP certificates to provide to MRA partner authorities Member States inspectorates should notify all MRA partners when serious GMP non-compliance has been discovered.

5.9 Where an inspection of an active substance manufacturer has been carried out at the request of the EDQM in connection with the CEP scheme and serious GMP non-compliance is revealed the inspectors involved should bear in mind that they have a dual responsibility. They should follow the procedures established by EDQM to determine the consequences for the CEP(s) in question, and they have an obligation to the Community to follow this procedure for notifying the serious GMP non-compliance. Every effort should be made to issue the non-compliance statement at the same time as the notification from EDQM concerning affected CEPs.

5.10 In cases where a CEP has been voided for non-GMP reasons EDQM notifies all national competent authorities using the agreed contact points. In its notification EDQM should indicate the reasons for voiding in order that authorities receiving the information can decide whether the quality, safety or efficacy of medicinal products already on the market is adversely affected and whether therefore a rapid alert is needed.

5.11 If the authority reporting the serious GMP non-compliance considers it necessary to remove products or certain batches from the market, it is responsible for issuing the Rapid Alert.
5.12 In the event that a rapid alert is necessary in response to CEP voiding or suspension in the circumstances mentioned in 5.9, 5.10 and 7.2, responsibility for issuing the rapid alert is as follows:

- For affected products subject to the Decentralised or Mutual Recognition procedures the Reference Member State,
- For centrally authorised products, the European Medicines Agency will co-ordinate in the same way as a quality defect.
- For products subject to national marketing authorisations only, a national recall may suffice. No rapid alert is necessary unless under the specific circumstances it is concluded that a class 1 defect is being handled, or, it is likely that the batches in question are on the market in other Member States.

5.13 Where the agreed action is suspension of a clinical trial each National Competent Authority authorising the trial in question should make appropriate entry into the EudraCT database.

6. Types and Consequences of Administrative Action

Some actions may lead to consequential actions. For example if a manufacturing authorisation is revoked or suspended or a CEP is voided or suspended it will have an impact on one or more marketing authorisations. Serious GMP non-compliance found at an active substance manufacturer means that manufacturing authorisation holders using the active substance in question as a starting material have failed to fulfil their legal obligations and therefore action may be taken against the manufacturing or import authorisation or QPs connected with it.

One or more of the following actions is/are possible. It is stressed that these are options and the Member States should take measures that are the most appropriate to the specific circumstances:

6.1 A Community notification of GMP non-compliance

6.1.1 Subject to the exceptions outlined in 6.1.2 an entry of non-compliance must be made into the EudraGMP database.

6.1.2 Community notification of serious GMP non-compliance is not necessary where the action to be taken is of no interest to any other Member State. Examples include:

- Action restricted to disciplining a QP
- Action restricted to refusal to grant a manufacturing or import authorisation or application to vary a such an authorisation
- For manufacturers or importers located in the Community, action limited to the issue of a restricted GMP certificate without corresponding action being deemed necessary, at the time, with regard to the relevant manufacturing or import authorisation.

Note: Such action would allow continued manufacture or importation but would put pressure on the authorisation holder concerned to take corrective action before steps against the manufacturing or import authorisation are taken, and the remainder of this procedure invoked. This approach is not suitable for manufacturers located in third countries since the close level of supervision implied is not feasible. Furthermore the GMP certificate for a third country manufacturer carries more weight within the Community regulatory system than it does for manufacturers subject to a Community manufacturing authorisation, where the manufacturing authorisation is the primary means of confirming GMP compliance.
6.2 Withdrawal of GMP certificate or Issue of GMP certificate with restricted scope

6.2.1 Existing valid GMP certificates with conflicting information will be superseded and should therefore be withdrawn in accordance with the Community procedure for the issue and update of GMP certificates. In some cases if the non-compliance is partial e.g. involving a limited category of dosage forms a new GMP certificate might also be issued, but restricted as appropriate.

6.2.2 A GMP certificate may be restricted for reasons other than serious GMP non-compliance, for example where a third country manufacturer is only partly inspected. However if a certificate is restricted because of serious non-compliance then this procedure must be followed and a notification of non-compliance entered into EudraGMP, unless section 6.1.2 applies.

6.3 Action against a manufacturing or import authorisation

6.3.1 Except in the specific circumstances described in section 6.1.2, consequential administrative action will be required for any directly affected manufacturing or import authorisation; otherwise there will be an unintentional inconsistency in the information available in the EudraGMP database.

6.3.2 The actions against a manufacturing or import authorisation may involve the following:

6.3.2.a. Refusal to grant a manufacturing or import authorisation or an application to vary a manufacturing authorisation

6.3.2.b. Total or partial suspension or revocation of manufacturing or import authorisation.

6.4 Voiding or suspension of CEP

6.4.1 EDQM is responsible for actions directly involving CEPs. However, if a CEP is voided, marketing authorisations depending solely on the CEP are invalid and should be suspended until the dossier is supplemented through variation with new information on the active substance. If the grounds for voiding the CEP are related to GMP non-compliance then an alternative active substance manufacturer would need to be added through a variation unless an alternative active substance manufacturer is already authorised, in which case the non-compliant active substance manufacturer should be removed through a variation.

6.4.2. CEPs may be voided for reasons unrelated to inspections, for example failure to fulfil critical commitments. Upon such notification by EDQM, each Competent Authority should establish whether they have issued national marketing authorisations that depend on the CEP(s) in question, and, where relevant, whether it is a Reference Member State. The European Medicines Agency will assess any impact on centrally authorised products.
6.4.3 Marketing authorisations depending on the CEP are invalid and should be suspended until the dossier is supplemented through variation with new information on the active substance and should therefore be suspended, unless an alternative source of active substance is authorised which is unaffected by the voided CEP. The Reference Member State should take the initiative in taking action on marketing authorisations subject to the mutual recognition or de-centralised procedures. The European Medicines Agency will co-ordinate action relating to centralised products. Individual national competent authorities take action against the marketing authorisation in the case of products authorised solely on a national basis.

6.5 Action in connection with marketing authorisations

6.5.1 Actions that can be taken include refusal to grant a marketing authorisation or application for variation, suspension or revocation. A marketing authorisation holder may also decide to withdraw a marketing authorisation voluntarily.

6.5.2 In the context of this procedure actions against marketing authorisations may be a consequence of action against the manufacturing authorisation or as a result of suspension or voiding of a CEP. It is possible however that the most appropriate course of action is against the marketing authorisation(s) alone. For example, a marketing authorisation listing a seriously non-compliant third country manufacturing site may need to be suspended or revoked unless an alternative manufacturing site is already authorised. A seriously non-compliant third country manufacturing site may need to be removed from a marketing authorisation through a variation.

6.5.3 Automatically suspending marketing authorisations associated with a non-compliant manufacturing site, where no alternative manufacturing site is authorised may not always be the most appropriate approach since if the manufacturing activity is suspended then this alone should serve to protect public/animal health. If the suspension or revocation of the manufacturing authorisation is partial then not all marketing authorisations listing the site will be affected.

6.5.4 In this case the Reference Member State, for products subject to de-centralised or mutual recognition procedures, the European Commission in the case of centralised products, or the individual National Competent Authority in the case of products authorised on a national basis only takes action against the marketing authorisation.

6.6 Impact on clinical trials

6.6.1 If serious GMP non-compliance is discovered at the manufacturer or importer of investigational medicinal products the impact on any completed or ongoing clinical trials will need to be taken into account in the recommendations of the reporting inspectorate. Trials may need to be suspended. Furthermore in some cases the results of completed trials may be thrown into question. Interruption, suspension or prohibition of trial must be entered into EudraCT.

6.6.2 The authority that carried out the inspection should involve the sponsor as well as the manufacturer or importer in order to identify all affected trials. If trials are prematurely terminated appropriate entries in EudraCT must be made.
6.7 Rapid Alert

6.7.1 Based on the information in the inspection report the authority reporting the serious GMP non-compliance should decide, in addition to any other action, whether or not it is necessary to take action with respect to batches of affected product(s) already on the market or being used in clinical trials.

6.7.2 For CEP voiding by EDQM that is unrelated to the outcome of an inspection, the Reference Member State (or the European Medicines Agency in the exceptional case that centralised products are affected) should recommend whether any batches should be recalled and invoke any Rapid Alert based on the information provided by EDQM on the reasons for voiding or suspension in its notice of voiding/suspension or, if necessary, following discussion with EDQM.

6.7.3 In the context of this procedure responsibility for issuing a rapid alert is outlined in section 5.12.

6.8 Prohibition on supply

6.8.1 Based on the information in the inspection report the authority reporting the serious GMP non-compliance should decide, in addition to any other action, whether or not to recommend a prohibition on supply to prevent products or batches from being released to the market or for use in clinical trials.

6.9 Disciplinary measures against the Qualified Person(s)

6.9.1. This action can be taken by the Supervisory authority if deemed appropriate. In some cases it may be the only action considered necessary. If this is the only action taken there is no impact on other Member States (see 6.1.2).

7. Communication

7.1 Serious GMP non-compliance

7.1.1 Notification of serious GMP non-compliance should take place after national procedures for dealing with adverse inspection reports have been followed and the action recommended by the inspector ratified or alternative action decided upon.

7.1.2 In principle unilateral action by one Member State should be avoided, unless justified. In order to facilitate co-ordinated action at Community level, notification of serious GMP non-compliance should be made prior to the execution of any action. In so far as is possible, the authority that carried out the inspection revealing the non-compliance should establish the following as appropriate:

- the identity of Member States with products directly affected by the inspection findings
- where relevant, the Reference Member State(s)
- whether centrally authorised products are involved
- the identity of other Supervisory Authorities in the case of medicinal or investigational medicinal products
- For investigational medicinal products the EudraCT trial reference numbers should be identified
- In the case of active substance manufacturer whether CEPs are affected in addition to marketing authorisations directly affected.
The authority that discovers the non-compliance should involve the manufacturer concerned, the importer and trial sponsor as appropriate to gather this information. It may be necessary to issue the notice of non-compliance without complete information if the risk to patient health is considered particularly severe.

7.1.3 Where there is more than one Supervisory Authority they should all be consulted by the reporting authority on proposed actions before wider transmission of the non-compliance information.

7.1.4 The agreed Community GMP non-compliance format should be used to report the non-compliance information to the EudraGMP database. The rapid alert distribution list should be used for this purpose.

7.1.5 The GMP non-compliance notification should explain the nature of any proposed action, or where justified, action already taken.

7.1.6 Any further communication with the issuing authority requesting clarification the non-compliance or providing relevant data, should be made via EudraGMP. All these questions and answers will then be available to all NCAs.

7.1.7 Where relevant, a contact telephone number should be given in the notification form together with a proposed time and date for a teleconference in which all affected member states can join, and in which co-ordinated action can be ratified. EDQM should be invited to join the teleconference if a CEP is affected.

7.1.8 The outcome of the teleconference, if held, should be communicated in a follow up message to confirm that the recommended action in the initial notification was agreed or to communicate any other agreed Community action. EudraGMP will be used for this once this module is operational.

7.1.9 If an inspection of an active substance manufacturer has been carried out other than at the request of EDQM and serious non-compliance is found, EDQM should be included in the communication of the serious non-compliance, unless it is clear that no CEPs are affected.

7.1.10 MRA partners are obliged to notify recipients of GMP certificates issued in the context of the MRA withdrawing those certificates if serious non-compliance is discovered. Third countries with which the Community has concluded an arrangement and which have been given access to EudraGMP will be notified automatically of GMP non-compliance statements placed into the database.

7.1.11 The issuing authority may be modified the non-compliance information entered in EudraGMP, if necessary. Any new modification of the non-compliance information should be distributed to the rapid alert distribution list.

7.2 Voiding of CEPs for non-GMP reasons

7.2.1 In cases where a CEP has been voided for non-GMP reasons EDQM notifies all national competent authorities using the agreed contact points. In its notification EDQM should indicate the reasons for voiding in order that authorities receiving the information can decide whether the quality, safety or efficacy of medicinal products already on the market is adversely affected and whether therefore a rapid alert is needed. Responsibilities are defined in 5.12.
8. Procedure Post-communication: Serious GMP Non-compliance

8.1 On receipt of a form notifying serious GMP non-compliance, either by fax or through EudraGMP, authorities should check whether nationally authorised products on their own territories are affected, and whether they are the Reference Member State for any affected products, seeking assistance from the inspectorate carrying out the inspection, if different, or the manufacturer(s) or importer(s) concerned as needed. If either applies, they should join the teleconference if there is to be one. If no teleconference is proposed, receiving authorities should, where appropriate, take the actions on its own territory that correspond with the actions proposed or already executed by the authority reporting the non-compliance. In the case of action against marketing authorisations subject to the de-centralised/mutual recognition procedures, the Reference Member State should take the initiative in following the recommendations of the Authority reporting the non-compliance. The European Medicines Agency will co-ordinate action relating to centralised products.

8.2 Disagreement with the actions proposed, if not resolved at the teleconference, should be dealt with through procedures established in accordance with Art. 122(90) of Directive 2001/83(2)/EC.

8.3 In the case of actions proposed for marketing authorisations subject to the De-centralised or Mutual Recognition procedures, CMD (h) or CMD (v) may decide to discuss the coordination of actions at a meeting of the relevant group before implementation.

8.4 Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Community action in connection with a marketing authorisation, or a rapid alert is not considered, on balance, to be in the interest of public health in any particular Member State, that Member State may decide to take alternative action to that proposed by the Member State initiating this procedure so long as this does not affect any other Member State. In such cases Art. 122(90) of Directive 2001/83(2)/EC obliges the Member State in question to notify the European Medicines Agency and the Commission. The Supervisory Authority or Reference Member State may find itself in this position but should nevertheless fulfil its responsibilities under section 5.

9. Legal References

Directive 2001/83(2)/EC Title XI (VIII) Supervision and Sanctions.

Directive 2001/83(2)/EC Title XIII (X) General Provisions.

Regulation (EC) No. 726/2004 Title II Chapter 2 Supervision and Penalties, Title III Chapter 2 Supervision and Sanctions.

Annex 1 - Action of Authority Discovering GMP Non-Compliance

*MIA = Manufacturing / Import Authorisation

1 If action against marketing authorisations is under consideration, the action ratified is that regarded as appropriate for the Community. If the reporting authority is not the Supervisory Authority the Supervisory Authority must be involved in the decision process.

2 Via EudraGMP

3 This is the starting point for CEPs voided for reasons unrelated to a GMP inspection.

4 If a CEP is involved EDQM is invited to join. If desired coordination of action in respect of marketing authorisations subject to the mutual recognition or de-centralised procedures may be discussed at the next meeting of CMD(h) or CMD(v-).
Annex 2 - Action by Authorities following Receipt of Information of GMP Non-Compliance

1 For centralised products the European Medicines Agency co-ordinates action.
2 Reference Member States should take the agreed action at Community level.
3 Notwithstanding appropriate responses to consequential rapid alerts or other consequential actions agreed at Community level.
Procedures Related to GMP Inspections

Procedure for Dealing with Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations

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Procedure for Dealing with Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations

1. Summary

1.1. A consolidated procedure for dealing with all circumstances of serious GMP non-compliance information originating from third country authorities and international organisations is necessary to ensure a coordinated approach to potential risks to public/animal health. Information may refer to API, finished product or IMP manufacturers and/or QC labs located either in the EU/EEA or in a third country.

1.2. This document supplements the procedure in the Compilation of Community Procedures (CoCP) for dealing with serious GMP non-compliance, with regard to the receipt, dissemination and initial assessment of serious GMP non-compliance notifications which originate from third country (non-EU, non-MRA) authorities or international organisations (e.g. WHO).

1.3. The procedure requires the Competent Authorities in the EEA involved in the receipt and coordination of serious GMP non-compliance notifications to disseminate relevant information to all other authorities in the Community in a timely manner, to enable the scope and impact of the notification to be confirmed, and subsequent recommendations for action to be made.

1.4. Communication with authorities of those countries with which the Community has made appropriate arrangements on GMP (e.g. MRA) may also be necessary.

2. Definitions

2.1. For the purposes of this procedure, serious GMP non-compliance is non-compliance with GMP that in the opinion of the reporting authority is of such a nature that administrative action is necessary to remove a potential risk to public/animal health. It should be noted that authorities in Third Countries issuing information may not share the same understanding.

3. Principles

3.1. Notification of serious GMP non-compliance from a third country authority or an international organisation should be assessed to determine the impact with respect to medicinal products supplied to the Community. It is possible that the detailed GMP non-compliances identified in the notification may have limited or no impact on EU products, e.g.:
   - in cases where the issues relate to facilities or products which are not involved in EU supply, or
   - where the non-compliances do not relate to the principles and guidelines of GMP as defined in the relevant Directives and as interpreted in Guidelines on GMP published by the European Commission in Eudralex Volume 4, or
   - Where the impact of the identified non-compliances, as interpreted in Guidelines on GMP published in Eudralex Volume 4, do not pose a significant risk to the quality or safety of products for EU supply.

   It is therefore important to determine the degree of Community impact as soon as possible following the initial notification.

3.2. Action following the notification of any non-compliance should be commensurate with the level of risk. Confirmation of serious non-compliance with the principles and guidelines of EU GMP by definition requires administrative action to be taken. Notification of GMP deficiencies which do not require administrative action should be recorded in the relevant Supervisory Authority's model for risk based inspection planning, in accordance with CoCP.
3.3. The notification of serious GMP non-compliance may have implications not only for the Member State receiving the notification but also other, possibly all, Member States. Therefore a mechanism that ensures consistent, co-ordinated action throughout the Community is important, even though the final outcome may differ based on specific national factors.

4. Scope

4.1. This procedure relates to the receipt, dissemination and initial assessment of information relating to serious GMP non-compliance received from third country authorities. If, following assessment of the notification, the nature and severity of non-compliance is considered to pose a potential risk to public or animal health, coordinated administrative action applicable to the situation should be considered in accordance with the detailed guidance provided in CoCP. Procedures should require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

4.2. This procedure applies to all notifications of serious GMP non-compliance discovered by a third country authority or international organisations either in the territory of an EEA Supervisory Authority or in third countries. It applies to inspections of active substance manufacturers, manufacturers or importers of medicinal products, manufacturers or importers of investigational medicinal products as well as quality control laboratories.

4.3. Notifications of serious non-compliance with Good Practice in the case of human blood, blood components or tissues, when used as a starting material in medicinal products, may also follow this procedure.

4.4. All serious GMP non-compliance relating to active substance manufacturers and all types of manufacturers located in third countries must be communicated even if it is known that no other Member State has an interest at the time as it may be important for all Member States to have the information available in the future.

5. Procedure and Responsibilities

5.1. Receipt of third country Authority notification.

5.1.1. A Member State who receives notification from a third country authority relating to serious GMP non-compliance at a manufacturer should ensure that sufficient information is obtained to permit an assessment of Community impact. Information should be collected using the format given in Appendix 1. The information to be recorded in this template includes:
- Contact details of single point of contact (SPoC) from the notifying authority
- Manufacturer name and address
- SPoC for manufacturer
- Product-related information
  - Human / Veterinary / IMP / API / export only
  - Products / dosage forms / buildings / lines affected
  - Centralised / DC / MRP / national marketing authorisations / products not subject to a MA
- Non-compliance issues
  - EU GMP non-compliances
  - Third country GMP non-compliances

5.1.2. The Member State which receives the initial notification may need to request further information from either the notifying third country authority, or the manufacturing site to which the notification refers, in order to ensure that the original information can be validated, and that sufficient information is obtained to permit an impact assessment in all Member States.

5.1.3. If an EU National Competent Authority receives a third country notification which refers to a manufacturer in its own territory, the notified National Competent Authority will take the necessary action. If the notification refers to a site in a different EU Member State, the notified National Competent Authority will forward the information to the National Competent Authority of the Member State in which the manufacturing site is located.

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1 Without prejudice to any confidentiality arrangements.
5.1.4. If the third country authority notification refers to a site in a third country, the Member State who receives the initial non-compliance notification is responsible for dissemination to all EU Member States and EMA, using the rapid alert single point of contact (SPoC) list¹.

5.1.5. Member States may receive further updates to the initial notification as additional information becomes available. These updates should also be circulated to ensure continuity of the information chain.

5.1.6. Each EU Competent Authority should have an internal national procedure to review this type of non-compliance information and determine whether there is any potential impact to products on their territory. Information relating to these products should be forwarded to the Member State who received the initial notification for collation, including information regarding product criticality (e.g. market share, and known availability of therapeutic alternatives).

5.1.7. The Member State who received the initial notification is responsible for arranging a teleconference with the concerned Member States to decide on the lead and on next steps. The selection of the coordinating Competent Authority will be based on a hierarchy of factors such as:

<table>
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<th>Product type</th>
<th>Coordinator</th>
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<td>Centralised Product</td>
<td>Supervisory Authority will lead; EMA will coordinate actions.</td>
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<td>DC / MRP</td>
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<td>Supervisory Authority of API site / Coordinator responsible for the product type containing the affected API(s)</td>
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5.1.8. In cases where there are no EU-coordinated marketing authorisations but there are various National Authorisations affecting more than one Member State, the coordinating Competent Authority will be determined on the basis of product criticality or market volume. Consideration should also be given to inclusion of the Competent Authorities previously involved in GMP inspections of the site, as the Authority that has carried out previous inspections will be best placed to assess the potential impact of the level of GMP non-compliance discovered.

5.1.9. Contact details for the coordinating Competent Authority SPoC should be sent to the notifying third country authority and the manufacturing site to which the notification refers.

5.1.10. If additional information becomes available during the process which indicates that a change in coordinating Competent Authority is appropriate (e.g. due to supplementary information on affected products), this should be agreed between the initial coordinator and the proposed new coordinator. Contact details of the new coordinator should be sent to the concerned Member States, and the contacts listed in section 5.1.8 above. Care should be taken to ensure that a change in coordinator is made only where absolutely necessary, and should be clearly communicated, in order to protect against confusion or delays in the assessment process.

5.1.11. The coordinating Competent Authority should continue to gather further information and clarification on the detailed inspection findings, impact on EU GMP and public/animal health. Coordination of issues with Marketing Authorisation Holders (MAH) may be required at this point, in order to determine potential impact on maintaining supplies. In cases where product is certified to the market by the holder of a Manufacturing and Import Authorisation who is not the MAH, information should also be obtained from the Qualified Person. Following collation of detailed GMP non-compliance and product related information, a risk assessment should be performed to determine the actions to be taken. Further guidance on the administrative actions available for consideration is described in CoCP.

¹ Without prejudice to any confidentiality arrangements.
5.1.12. Consideration should be given with regards to whether an EU GMP inspection should be performed prior to taking any administrative action, or whether the significance of the issues notified require immediate action in the interest of public/animal health.

5.1.13. If the initial dissemination of information by the Member State which received the initial notification indicated that more than one Member State is affected by the notification of serious GMP non-compliance, a contact telephone number should be provided by the coordinating Competent Authority, together with a proposed time and date for a teleconference in which all affected Member States can join. This will assist in ratification of proposed administrative action. EDQM should be invited to join the teleconference if a CEP is affected.

5.1.14. The coordinating Competent Authority will be responsible for communicating the agreed administrative actions to the affected Member States using the template provided in Appendix 1.

5.1.15. The procedure post-communication should be followed as described in CoCP. An EU GMP inspection should be performed in order to verify the third country notification of non-compliances before consideration of issuing a statement of serious GMP non-compliance. In cases where this is not possible due to a perceived enhanced physical threat to inspectors (for political reasons, health reasons or others), the use of a 'distant assessment', as described in CoCP may be an appropriate alternative means to inform the decision regarding the issuance of a statement of serious GMP non-compliance.
Procedures Related to Inspections of Wholesale Distributors

Guideline on Training and Qualification of Inspectors Performing Inspections of Wholesale Distributors

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<td>Date of adoption</td>
<td>November 2010</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>1 April 2011</td>
</tr>
<tr>
<td>Supersedes</td>
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<td>Notes</td>
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</tbody>
</table>
Guideline on Training and Qualification of Inspectors Performing Inspections of Wholesale Distributors

1. Summary

Taking into account the paramount importance of the management of inspection services, this guideline establishes some requirements concerning experience, training and qualifications of inspectors performing inspections of wholesale distributors.

Objectivity, confidentiality, professional integrity, knowledge of technical matters, knowledge of legislation, and auditing skills are the main requirements of inspectors.

Inspectors should be very well trained in all aspects of the distribution of medicinal products and in the way of conducting an inspection.

The guideline provides information on minimal requirements and is intended to be supplementary to any national requirements.

2. Scope

This guideline defines the training and qualification criteria required for an inspector who shall conduct an inspection to verify compliance with the legal requirements relating to wholesale distribution for the competent authority of the Member State concerned. It also identifies ongoing training needs of inspectors as they progress from ‘entry level’ to ‘expert’ across a number of inspection specialities, each speciality having their own specific technical, legislative and practical inspection training needs.

3. Background

3.1 General Aspects

Member States should appoint inspectors to inspect wholesale distributor sites concerned by Directive 2001/83/EC and 2001/82/EC. There should be sufficient resources at all levels to meet, effectively and efficiently, the EU requirements of verifying compliance with the legal requirements relating to the wholesale distribution of medicinal products.

The inspectors shall be officials of or appointed by the competent authorities of the Member States in accordance with national regulations and follow the provisions for the national competent authority.

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1 This includes compliance with Good Distribution Practice in the case of medicinal products for human use.
All inspectors should be competent to carry out their assigned duties and receive appropriate training. When needed teams of inspectors may be nominated comprising inspectors with appropriate qualifications and experience to collectively fulfil the requirements necessary for conducting the inspection.

The inspectors should be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of inspections according to applicable national laws or European requirements.

3.2 Personal Qualities

The personal skills of an inspector are important in helping to achieve the objectives of the inspections.

During an inspection the inspector should help in creating a positive atmosphere. Inspectors need to remain objective during the inspection and in this context should answer questions or provide clarification but avoid entering into the role of a consultant.

The inspector should have a high personal integrity, maturity, be open-minded, understanding of complexity, possess sound judgement, assertiveness, analytical skills and tenacity and have the ability to perceive situations in a realistic way.

The inspector should have demonstrated competence in clearly and fluently expressing concepts and ideas orally and in writing in their official recognized language.

4. Qualification and Training

4.1 Qualification

Inspectors shall be qualified according to national requirements.

4.2 Training

The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for planning, carrying out and reporting inspections.

Training and experience should be documented individually and evaluated within the requirements of the applicable quality system of the Competent Authority/Inspectorate.

4.2.1 Basic Training

Inspectors should be capable of demonstrating their understanding of relevant matters in the regulatory field, including:

- Good Distribution Practice (GDP)
- Good Manufacturing Practices (GMP) basic knowledge
- Applicable EU and national legislation
- Knowledge of the Compilation of Community Procedures
- Knowledge of the organisation and quality system of the national competent authorities
- Knowledge of wholesaling principles and roles of actors in the supply chain
• The general principles of Quality Management Systems
• Marketing, manufacturing and wholesale distribution authorisation systems and their relationships
• Inspection techniques including skills required for managing an inspection, such as planning, organising, and evaluation of findings and reporting, communicating or providing feedback to the inspectee. These may be acquired by attending relevant course(s) and/or by accompanying and/or be guided by senior inspectors during inspections
• Interrelation of inspection, sampling and analysis, and licensing, as appropriate
• An awareness of trends in falsified medicines

4.2.2 In-Service Training

After recruitment and in addition to their basic training, new inspectors should be trained by an assigned mentor. The theory of inspection should be explained and the practice should be shown in the field, so that concrete examples of the meaning and of the goals of inspections are given and can be discussed. New inspectors should participate but only as observers, in on the spot inspections carried out during their basic training.

Besides this and where needed, training courses in auditing techniques and communications, reporting, languages, legal matters and management should be organised by national inspectorates.

Prior to assuming responsibility for performing inspections of wholesale distributors the new inspector should have gained experience by participation as team member in inspections led by a senior inspector. Preferably, the inspector should start with inspections as a member of a team and then deal progressively with more complex inspections to be able to act as a team leader. This should be recorded within the requirements of the applicable quality systems of the Competent Authority/Inspectorate.

The inspector should, through suitable means, demonstrate his or her knowledge and capability of using the necessary management skills required in execution of an inspection, i.e. planning, announcing, conducting and reporting an inspection.

The inspector should document and demonstrate his or her capability to write inspection reports according to both EU and national requirements.

4.2.3 Continuous Training

Considering the expanding technologies in the wholesale distribution arena, the ever more frequent utilisation of automatic and computerised systems such as warehouse inventory management systems, inspectors should also receive continuous training. This could be achieved through participation in courses, seminars, meetings and conferences organised either by the national inspectorates or by national or international scientific organisations. When appropriate, joint inspections or training visits with other inspectors of the same Member State or of other Member States may be a useful training tool.
All inspectors performing inspections of wholesale distributors should aim to spend five days training per year. GDP aspects should be covered in this training. This ongoing training may include training inspections, courses, symposia, conferences, etc. These training days should be planned and documented.

5. Maintenance of Competence

Inspectors should have their performance and qualifications periodically reviewed and assessed within the requirements of the applicable quality system of the Competent Authority/Inspectorate. Their competence should be maintained and updated by continuous training as described in 4.2.3. This should be documented and its effectiveness assessed.

6. Harmonisation within the EEA

In order to promote international harmonisation in the interpretation of the principles and compliance, the wholesale distribution inspection program management should facilitate training activities, including on the job training, at national and international levels.

Consultations with the staff of other inspectorates and joint inspections or training visits are encouraged and may be used as a training method.

The Competent Authority/Inspectorate should also facilitate and encourage the exchange of information and practical experience gained by inspectors in the field of wholesale distribution.

7. Legal References

Directive 2001/83/EC and 201/82/EC

Forms Used by Regulators

GMP Inspection Report – Union Format

Table of contents:

- GMP Inspection report - Union format
- Definition of Significant Deficiencies

<table>
<thead>
<tr>
<th>Title</th>
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<td>31 January 2010</td>
</tr>
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<td>Date of entry into force</td>
<td>1 August 2010</td>
</tr>
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<td>Supersedes</td>
<td>Version in force from October 2005</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>The format was aligned with activities and amendments made in order to enable summary reports for European Medicines Agency inspections to be discontinued</td>
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</tbody>
</table>
**GMP Inspection Report - Union Format**

**Report Reference no.:**

**Name of product(s) and pharmaceutical form(s):** Essential for inspections requested by the European Medicines Agency otherwise only necessary for product specific inspections.

**Inspected site(s):** Name and full address of the inspected site, including exact location/designation of the production facilities inspected. EudraGMP reference number Site location identifier (DUNS number/GPS coordinates)

**Activities carried out:**

<table>
<thead>
<tr>
<th>Human</th>
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<th>IMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture of finished products</td>
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<tr>
<td>Sterile</td>
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<tr>
<td>Non-sterile</td>
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<tr>
<td>Biologicals</td>
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<tr>
<td>Sterilisation of excipient, active substance or medicinal product</td>
<td></td>
<td></td>
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<tr>
<td>Primary packaging</td>
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<td></td>
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<tr>
<td>Secondary packaging</td>
<td></td>
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<tr>
<td>Quality control testing</td>
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<tr>
<td>Importing</td>
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<td>Batch certification</td>
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<tr>
<td>Storage and distribution</td>
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<tr>
<td>Manufacture of active substance</td>
<td></td>
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<tr>
<td>Other ______________________</td>
<td></td>
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</tbody>
</table>

**Inspection date(s):** Date(s), month, year.

**Inspector(s) and Expert(s):** Name(s) of the inspector(s). Name(s) of expert / assessor (if applicable). Name(s) of the Competent Authority(ies).

**References:** Reference number of marketing and / or manufacturing authorisations. EMEA reference number(s) if the inspection is requested by the European Medicines Agency.

**Introduction:** Short description of the company and the activities of the company. For inspections in non-EEA countries, it should be stated whether the Competent Authority of the country, where the inspection took place, was informed of the inspection and whether the Competent Authority took part in the inspection. Date of previous inspection. Name(s) of inspector(s) involved in previous inspection. Major changes since the previous inspection.

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1 The Union format for a GMP inspection report has been established in accordance with Art. 47 of Directive 2004/27/EC and Art. 51 of Directive 2004/28/EC amending Directives 2001/83/EC and 2001/82/EC respectively.
**Brief report of the inspection activities undertaken:**

<table>
<thead>
<tr>
<th>Scope of Inspection:</th>
<th>Short description of the inspection (product related, process related inspection and/or general GMP inspection, reference to specific dosage forms where appropriate). The reason for the inspection should be specified (e.g. new marketing application, routine, investigation of product defect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspected area(s) and main steps/history of the inspection</td>
<td>Each inspected area should be specified.</td>
</tr>
<tr>
<td>Activities not inspected:</td>
<td>Where necessary attention should be drawn to areas or activities not subject to inspection on this occasion.</td>
</tr>
<tr>
<td>Personnel met during the inspection:</td>
<td>The names and titles of key personnel met should be specified (listed in annex).</td>
</tr>
<tr>
<td>Inspectors findings and observations relevant to the inspection; and deficiencies:</td>
<td>Relevant headings from The Rules Governing Medicinal Products in the European Community, Good Manufacturing Practice for Medicinal Products Vol. IV. This section can link the findings to the deficiencies and be used to explain classification. The detail in the narrative of this section of the report may be reduced where a Site Master File acceptable to the reporting authority has been submitted to the Competent Authority.</td>
</tr>
<tr>
<td>Heads to be used</td>
<td>Overview of inspection findings from last inspection and the corrective action taken.</td>
</tr>
<tr>
<td>New headings may be introduced when relevant</td>
<td>Quality Management, Personnel, Premises and Equipment, Documentation, Production, Quality Control, Contract Manufacture and Analysis, Complaints and Product Recall, Self Inspection</td>
</tr>
<tr>
<td>Distribution and shipment:</td>
<td>e.g. Compliance with Good Distribution Practice</td>
</tr>
<tr>
<td>Questions raised relating to the assessment of a marketing application:</td>
<td>e.g. Pre-authorisation inspections</td>
</tr>
<tr>
<td>Other specific issues identified:</td>
<td>e.g. Relevant future changes announced by company</td>
</tr>
<tr>
<td>Site Master File:</td>
<td>Assessment of SMF if any; date of SMF</td>
</tr>
<tr>
<td>Miscellaneous:</td>
<td></td>
</tr>
<tr>
<td>Samples taken</td>
<td></td>
</tr>
<tr>
<td>Annexes attached:</td>
<td>List of any annexes attached</td>
</tr>
</tbody>
</table>
### List of deficiencies classified into critical, major and others:

All deficiencies should be listed and the relevant reference to the EU GMP Guide and other relevant EU Guidelines should be mentioned.

All deficiencies found should be listed even if corrective action has taken place straight away.

If the deficiencies are related to the assessment of the marketing application it should be clearly stated.

The company should be asked to inform the Inspectorate about the proposed time schedule for corrections and on progress.

### Inspectors’ comments on the manufacturer’s response to the inspection findings:

i.e. are the responses acceptable?

### Inspectors’ comments on the questions/issues raised in the assessment report

### Recommendations for further actions (if any):

To the Committee requesting the inspection or to the Competent / Enforcement Authority for the site inspected.

### Summary and conclusions:

The inspector(s) should state whether, within the scope of the inspection, the manufacturer or importer operates in general compliance with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC, or not, and whether the manufacturer or importer is acceptable for the products in question. (This would apply to situations where there is a degree of non-compliance but where a corrective action plan has been agreed and the inspector has no reason to believe that it will not be implemented and where there is no immediate threat to public health).

### Name(s):

The inspection report should be signed and dated by all inspector(s)/assessors having participated in the inspection.

### Signatures(s):

### Organisation(s):

### Date:

### Distribution of Report:

For inspections requested by the European Medicines Agency the inspection report should be forwarded to the Agency.
Definition of Significant Deficiencies

1. Critical Deficiency:
   A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2. Major Deficiency:
   A non-critical deficiency:
   
   - which has produced or may produce a product, which does not comply with its marketing authorisation;
   - which indicates a major deviation from EU Good Manufacturing Practice;
   - (within EU) which indicates a major deviation from the terms of the manufacturing authorisation;
   - which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;
   - a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such;

3. Other Deficiency:
   A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

   (A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).
Forms used by Regulators

Union Basic Format for Manufacturer’s Authorisation

Table of contents:

- Union Format for Manufacturers Authorisation
- ANNEXES 1and/or 2- Scope of Authorisation
- ANNEX 3 (Optional) - Address(es) of Contract Manufacturing Sites
- ANNEX 4 (Optional) - Address(es) of Contract Laboratories
- ANNEX 5 (Optional) - Name of Qualified Person
- ANNEX 6 (Optional) - Name of person responsible for quality control / production
- ANNEX 7 (Optional) - Date of Inspection on which authorisation granted
- ANNEX 8 (Optional) - Products authorised for manufacture/import

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<th>Title</th>
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<td>By 2 January 2013</td>
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<td>Reason for revision</td>
<td>Modifications were introduced to facilitate harmonised interpretation.</td>
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<td>Notes</td>
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</table>
Union Format for Manufacturer’s Authorisation

1. Authorisation number

2. Name of authorisation holder

3. Address(es) of manufacturing site(s)
   (All authorised sites should be listed if not covered by separate licences)

4. Legally registered address of authorisation holder

5. Scope of authorisation and dosage forms
   ANNEX 1 and/or ANNEX 2
   (Separate Annexes for different sites should be used if not covered by separate licences)

6. Legal basis of authorisation

7. Name of responsible officer of the competent authority of the member state granting the manufacturing authorisation

8. Signature

9. Date

10. Annexes attached
    Annex 1 and/or Annex 2
    Optional Annexes as required:
    Annex 3 (Addresses of Contract Manufacturing Site(s))
    Annex 4 (Addresses of Contract Laboratories)
    Annex 5 (Name of Qualified Person)
    Annex 6 (Name of responsible persons)
    Annex 7 (Date of inspection on which authorisation granted, scope of last inspection)
    Annex 8 (Manufactured/imported products authorised)

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1 The authorisation referred to in paragraph 40(1) of Directive 2001/83/EC and 44(1) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.

2 Guidance on the interpretation of this template can be found in the Help menu of EudraGMP database.

3 The Competent Authority is responsible for appropriate linking of the authorisation with the manufacturer’s application (Art. 42(3) of Directive 2001/83/EC and Art. 46(3) of Directive 2001/82/EC as amended).
SCOPE OF AUTHORISATION (delete the sections that do not apply) ANNEX 1

Name and address of the site:

- Human Medicinal Products
- Veterinary Medicinal Products

AUTHORISED OPERATIONS

- Manufacturing Operations (according to part 1)
- Importation of Medicinal Products (according to part 2)

Part 1 - MANUFACTURING OPERATIONS

1.1 Sterile products

1.1.1 Aseptically prepared (processing operations for the following dosage forms)

1.1.1.1 Large volume liquids
1.1.1.2 Lyophilisates
1.1.1.3 Semi-solids
1.1.1.4 Small volume liquids
1.1.1.5 Solids and implants
1.1.1.6 Other aseptically prepared products <free text>

1.1.2 Terminally sterilised (processing operations for the following dosage forms)
1.1.2.1 Large volume liquids
1.1.2.2 Semi-solids
1.1.2.3 Small volume liquids
1.1.2.4 Solids and implants
1.1.2.5 Other terminally sterilised prepared products <free text>

1.1.3 Batch certification
1.2 **Non-sterile products**

1.2.1 *Non-sterile products (processing operations for the following dosage forms)*

- 1.2.1.1 Capsules, hard shell
- 1.2.1.2 Capsules, soft shell
- 1.2.1.3 Chewing gums
- 1.2.1.4 Impregnated matrices
- 1.2.1.5 Liquids for external use
- 1.2.1.6 Liquids for internal use
- 1.2.1.7 Medicinal gases
- 1.2.1.8 Other solid dosage forms
- 1.2.1.9 Pressurised preparations
- 1.2.1.10 Radionuclide generators
- 1.2.1.11 Semi-solids
- 1.2.1.12 Suppositories
- 1.2.1.13 Tablets
- 1.2.1.14 Transdermal patches
- 1.2.1.15 Intraruminal devices
- 1.2.1.16 Veterinary premixes
- 1.2.1.17 Other non-sterile medicinal product <free text>

1.2.2 **Batch Certification**

1.3 **Biological medicinal products**

1.3.1 *Biological medicinal products (list of product types)*

- 1.3.1.1 Blood products
- 1.3.1.2 Immunological products
- 1.3.1.3 Cell therapy products
- 1.3.1.4 Gene therapy products
- 1.3.1.5 Biotechnology products
- 1.3.1.6 Human or animal extracted products
- 1.3.1.7 Tissue engineered products
- 1.3.1.8 Other biological medicinal products <free text>

1.3.2 **Batch certification(list of product types)**

- 1.3.2.1 Blood products
- 1.3.2.2 Immunological products
- 1.3.2.3 Cell therapy products
- 1.3.2.4 Gene therapy products
- 1.3.2.5 Biotechnology products
- 1.3.2.6 Human or animal extracted products
- 1.3.2.7 Tissue engineered products
- 1.3.2.8 Other biological medicinal products <free text>

1.4 **Other products or manufacturing activity**

1.4.1 *Manufacture of:*

- 1.4.1.1 Herbal products
- 1.4.1.2 Homoeopathic products
- 1.4.1.3 Other <free text>

1.4.2 *Sterilisation of active substances/excipients/finished product:*

- 1.4.2.1 Filtration
- 1.4.2.2 Dry heat
- 1.4.2.3 Moist heat
- 1.4.2.4 Chemical
- 1.4.2.5 Gamma irradiation
- 1.4.2.6 Electron beam

1.4.3 *Other <free text>
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<td></td>
<td>1.5.1.1 Capsules, hard shell</td>
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<tr>
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<td>1.5.1.2 Capsules, soft shell</td>
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<td>1.5.1.3 Chewing gums</td>
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<td>1.5.1.16 Veterinary premixes</td>
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|     | 1.5.1.17 Other non-sterile medicinal products <free text:>

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<td>1.6.2 Microbiological: non-sterility</td>
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<td></td>
<td>1.6.3 Chemical/Physical</td>
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<td>1.6.4 Biological</td>
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Any restrictions or clarifying remarks related to the scope of these Manufacturing operations

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## Part 2 - IMPORTATION OF MEDICINAL PRODUCTS

### 2.1 Quality control testing of imported medicinal products

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<td>Microbiological: sterility</td>
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<td>2.1.2</td>
<td>Microbiological: non-sterility</td>
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<tr>
<td>2.1.3</td>
<td>Chemical/Physical</td>
</tr>
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<td>2.1.4</td>
<td>Biological</td>
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### 2.2 Batch certification of imported medicinal products

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<tr>
<th>Subsection</th>
<th>Description</th>
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<tbody>
<tr>
<td>2.2.1</td>
<td>Sterile Products</td>
</tr>
<tr>
<td>2.2.1.1</td>
<td>Aseptically prepared</td>
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<tr>
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<td>Terminally sterilised</td>
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<td>2.2.2</td>
<td>Non-sterile products</td>
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<td>2.2.3</td>
<td>Biological medicinal products</td>
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<tr>
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<td>Blood products</td>
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<tr>
<td>2.2.3.2</td>
<td>Immunological products</td>
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<td>2.2.3.3</td>
<td>Cell therapy products</td>
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<td>Gene therapy products</td>
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<td>2.2.3.5</td>
<td>Biotechnology products</td>
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<td>2.2.3.6</td>
<td>Human or animal extracted products</td>
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<tr>
<td>2.2.3.7</td>
<td>Tissue engineered products</td>
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<td>2.2.3.8</td>
<td>Other biological medicinal products &lt;free text&gt;</td>
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### 2.3 Other importation activities (any other importation activity that is not covered above)

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.1</td>
<td>Site of physical importation</td>
</tr>
<tr>
<td>2.3.2</td>
<td>Importation of intermediate which undergoes further processing</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Biological active substance</td>
</tr>
<tr>
<td>2.3.4</td>
<td>Other &lt;free text&gt;</td>
</tr>
</tbody>
</table>

Any restrictions or clarifying remarks related to the scope of these Importing operations

..............................................................................................................................................................................
..............................................................................................................................................................................
SCOPES OF AUTHORISATION (delete the sections that do not apply or use yes/no)

Name and address of the site:

☐ Human Investigational Medicinal Products (optional)

AUTHORISED OPERATIONS

☐ Manufacturing Operations of Investigational Medicinal Products (according to part 1)
☐ Importation of Investigational Medicinal Products (according to part 2)

Part 1 - MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS

1.1 Sterile investigational medicinal products

1.1.1 Aseptically prepared (processing operations for the following dosage forms)
   1.1.1.1 Large volume liquids
   1.1.1.2 Lyophilisates
   1.1.1.3 Semi-solids
   1.1.1.4 Small volume liquids
   1.1.1.5 Solids and implants
   1.1.1.6 Other aseptically prepared products <free text>

1.1.2 Terminally sterilised (processing operations for the following dosage forms)
   1.1.2.1 Large volume liquids
   1.1.2.2 Semi-solids
   1.1.2.3 Small volume liquids
   1.1.2.4 Solids and implants
   1.1.2.5 Other terminally sterilised prepared products <free text>

1.1.3 Batch certification
### 1.2 Non-sterile investigational medicinal products

#### 1.2.1 Non-sterile products (processing operations for the following dosage forms)

1.2.1.1 Capsules, hard shell
1.2.1.2 Capsules, soft shell
1.2.1.3 Chewing gums
1.2.1.4 Impregnated matrices
1.2.1.5 Liquids for external use
1.2.1.6 Liquids for internal use
1.2.1.7 Medicinal gases
1.2.1.8 Other solid dosage forms
1.2.1.9 Pressurised preparations
1.2.1.10 Radionuclide generators
1.2.1.11 Semi-solids
1.2.1.12 Suppositories
1.2.1.13 Tablets
1.2.1.14 Transdermal patches
1.2.1.15 Other non-sterile medicinal product <free text>

#### 1.2.2 Batch certification

### 1.3 Biological investigational medicinal products

#### 1.3.1 Biological medicinal products (list of product types)

1.3.1.1 Blood products
1.3.1.2 Immunological products
1.3.1.3 Cell therapy products
1.3.1.4 Gene therapy products
1.3.1.5 Biotechnology products
1.3.1.6 Human or animal extracted products
1.3.1.7 Tissue engineered products
1.3.1.8 Other biological medicinal products <free text>

#### 1.3.2 Batch certification (list of product types)

1.3.2.1 Blood products
1.3.2.2 Immunological products
1.3.2.3 Cell therapy products
1.3.2.4 Gene therapy products
1.3.2.5 Biotechnology products
1.3.2.6 Human or animal extracted products
1.3.2.7 Tissue engineered products
1.3.2.8 Other biological medicinal products <free text>

### 1.4 Other investigational medicinal products or manufacturing activity

#### 1.4.1 Manufacture of:

1.4.1.1 Herbal products
1.4.1.2 Homoeopathic products
1.4.1.3 Other <free text>

#### 1.4.2 Sterilisation of active substances/excipients/finished product:

1.4.2.1 Filtration
1.4.2.2 Dry heat
1.4.2.3 Moist heat
1.4.2.4 Chemical
1.4.2.5 Gamma irradiation
1.4.2.6 Electron beam

#### 1.4.3 Other <free text>
### 1.5 Packaging

#### 1.5.1 Primary packing
- 1.5.1.1 Capsules, hard shell
- 1.5.1.2 Capsules, soft shell
- 1.5.1.3 Chewing gums
- 1.5.1.4 Impregnated matrices
- 1.5.1.5 Liquids for external use
- 1.5.1.6 Liquids for internal use
- 1.5.1.7 Medicinal gases
- 1.5.1.8 Other solid dosage forms
- 1.5.1.9 Pressurised preparations
- 1.5.1.10 Radionuclide generators
- 1.5.1.11 Semi-solids
- 1.5.1.12 Suppositories
- 1.5.1.13 Tablets
- 1.5.1.14 Transdermal patches
- 1.5.1.15 Other non-sterile medicinal products <free text>

#### 1.5.2 Secondary packing

### 1.6 Quality control testing

#### 1.6.1 Microbiological: sterility

#### 1.6.2 Microbiological: non-sterility

#### 1.6.3 Chemical/Physical

#### 1.6.4 Biological

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations

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## Part 2 - IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS

### 2.1 Quality control testing of imported investigational medicinal products
- **2.1.1 Microbiological: sterility**
- **2.1.2 Microbiological: non-sterility**
- **2.1.3 Chemical/Physical**
- **2.1.4 Biological**

### 2.2 Batch certification of imported investigational medicinal products
- **2.2.1 Sterile Products**
  - **2.2.1.1 Aseptically prepared**
  - **2.2.1.2 Terminally sterilised**
- **2.2.2 Non-sterile products**
- **2.2.3 Biological products**
  - **2.2.3.1 Blood products**
  - **2.2.3.2 Immunological products**
  - **2.2.3.3 Cell therapy products**
  - **2.2.3.4 Gene therapy products**
  - **2.2.3.5 Biotechnology products**
  - **2.2.3.6 Human or animal extracted products**
  - **2.2.3.7 Tissue engineered products**
  - **2.2.3.8 Other biological medicinal products <free text>**

### 2.3 Other importation activities
- **2.3.1 Site of physical importation**
- **2.3.2 Importation of intermediate which undergoes further processing**
- **2.3.3 Biological active substance**
- **2.3.4 Other <free text>**

Any restrictions or clarifying remarks related to the scope of these Importing operations

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ANNEX 3 (Optional)

Address(es) of Contract Manufacturing Sites

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ANNEX 4 (Optional)

Address(es) of Contract Laboratories

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ANNEX 5 (Optional)

Name(s) of Qualified Person(s)

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ANNEX 6 (Optional)

Name(s) of person(s) responsible for quality control

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Name(s) of person(s) responsible for production

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### ANNEX 7 (Optional)

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ANNEX 8 (Optional)

Products authorised to be manufactured/imported (in accordance with Article 41 and 42 of Directive 2001/83/EC and/or Article 45 and 46 of Directive 2001/82/EC, as amended).

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Forms used by Regulators

Union Format for a GMP Certificate

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PART 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC or Art. 80(5) of Directive 2001/82/EC or Art. 15 of Directive 2001/20/EC* or

Issued under the provisions of the Mutual Recognition Agreement between the European Union and [MRA Partner]*

The competent authority of [Member State] confirms the following:

The manufacturer 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This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field.

This certificate is valid only when presented with all pages and both Parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMP. If it does not appear, please contact the issuing authority.
### Part 2

- Human Medicinal Products*
- Veterinary Medicinal Products*
- Human Investigational Medicinal Products*

### 1 MANUFACTURING OPERATIONS - MEDICINAL PRODUCTS*

#### 1.1 Sterile products

1.1.1 Aseptically prepared (processing operations for the following dosage forms)

- 1.1.1.1 Large volume liquids
- 1.1.1.2 Lyophilisates
- 1.1.1.3 Semi-solids
- 1.1.1.4 Small volume liquids
- 1.1.1.5 Solids and implants
- 1.1.1.6 Other aseptically prepared products <free text>

1.1.2 Terminally sterilised (processing operations for the following dosage forms)

- 1.1.2.1 Large volume liquids
- 1.1.2.2 Semi-solids
- 1.1.2.3 Small volume liquids
- 1.1.2.4 Solids and implants
- 1.1.2.5 Other terminally sterilised prepared products <free text>

1.1.3 Batch certification

#### 1.2 Non-sterile products

1.2.1 Non-sterile products (processing operations for the following dosage forms)

- 1.2.1.1 Capsules, hard shell
- 1.2.1.2 Capsules, soft shell
- 1.2.1.3 Chewing gums
- 1.2.1.4 Impregnated matrices
- 1.2.1.5 Liquids for external use
- 1.2.1.6 Liquids for internal use
- 1.2.1.7 Medicinal gases
- 1.2.1.8 Other solid dosage forms
- 1.2.1.9 Pressurised preparations
- 1.2.1.10 Radionuclide generators
- 1.2.1.11 Semi-solids
- 1.2.1.12 Suppositories
- 1.2.1.13 Tablets
- 1.2.1.14 Transdermal patches
- 1.2.1.15 Intraruminal devices
- 1.2.1.16 Veterinary premixes
- 1.2.1.17 Other non-sterile medicinal product <free text>

1.2.2 Batch certification
1.3 Biological medicinal products

1.3.1 Biological medicinal products
1.3.1.1 Blood products
1.3.1.2 Immunological products
1.3.1.3 Cell therapy products
1.3.1.4 Gene therapy products
1.3.1.5 Biotechnology products
1.3.1.6 Human or animal extracted products
1.3.1.7 Tissue engineered products
1.3.1.8 Other biological medicinal products <free text>

1.3.2 Batch certification (list of product types)
1.3.2.1 Blood products
1.3.2.2 Immunological products
1.3.2.3 Cell therapy products
1.3.2.4 Gene therapy products
1.3.2.5 Biotechnology products
1.3.2.6 Human or animal extracted products
1.3.2.7 Tissue engineered products
1.3.2.8 Other biological medicinal products <free text>

1.4 Other products or processing activity

1.4.1 Manufacture of:
1.4.1.1 Herbal products
1.4.1.2 Homoeopathic products
1.4.1.3 Other <free text>

1.4.2 Sterilisation of active substances/excipients/finished product:
1.4.2.1 Filtration
1.4.2.2 Dry heat
1.4.2.3 Moist heat
1.4.2.4 Chemical
1.4.2.5 Gamma irradiation
1.4.2.6 Electron beam
1.4.3 Others <free text>

1.5 Packaging

1.5.1 Primary packing
1.5.1.1 Capsules, hard shell
1.5.1.2 Capsules, soft shell
1.5.1.3 Chewing gums
1.5.1.4 Impregnated matrices
1.5.1.5 Liquids for external use
1.5.1.6 Liquids for internal use
1.5.1.7 Medicinal gases
1.5.1.8 Other solid dosage forms
1.5.1.9 Pressurised preparations
1.5.1.10 Radionuclide generators
1.5.1.11 Semi-solids
1.5.1.12 Suppositories
1.5.1.13 Tablets
1.5.1.14 Transdermal patches
1.5.1.15 Intraruminal devices
1.5.1.16 Veterinary premixes
1.5.1.17 Other non-sterile medicinal products <free text>

1.5.2 Secondary packing
### 1.6 Quality control testing

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<td>Chemical/Physical</td>
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<td>Biological</td>
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### 2 IMPORTATION OF MEDICINAL PRODUCTS*

#### 2.1 Quality control testing of imported medicinal products

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#### 2.2 Batch certification of imported medicinal products

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<td>2.2.2</td>
<td>Non-sterile products</td>
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<tr>
<td>2.2.3</td>
<td>Biological medicinal products</td>
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<td>2.2.3.1</td>
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<tr>
<td>2.2.3.2</td>
<td>Immunological products</td>
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<td>2.2.3.3</td>
<td>Cell therapy products</td>
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<tr>
<td>2.2.3.4</td>
<td>Gene therapy products</td>
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<tr>
<td>2.2.3.5</td>
<td>Biotechnology products</td>
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<tr>
<td>2.2.3.6</td>
<td>Human or animal extracted products</td>
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<td>2.2.3.7</td>
<td>Tissue engineered products</td>
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<td>2.2.3.8</td>
<td>Other biological medicinal products &lt;free text&gt;</td>
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#### 2.3 Other importation activities

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<td>2.3.1</td>
<td>Site of physical importation</td>
</tr>
<tr>
<td>2.3.2</td>
<td>Importation of intermediate which undergoes further processing</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Other &lt;free text&gt;</td>
</tr>
</tbody>
</table>

Any restrictions or clarifying remarks related to the scope of this certificate*:

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### 3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

**Active Substance(s):**

#### 3.1 Manufacture of Active Substance by Chemical Synthesis

- 3.1.1 Manufacture of active substance intermediates
- 3.1.2 Manufacture of crude active substance
- 3.1.3 Salt formation / Purification steps: <free text> (e.g. crystallisation)
- 3.1.4 Other <free text>

#### 3.2 Extraction of Active Substance from Natural Sources

- 3.2.1 Extraction of substance from plant source
- 3.2.2 Extraction of substance from animal source
- 3.2.3 Extraction of substance from human source
- 3.2.4 Extraction of substance from mineral source
- 3.2.5 Modification of extracted substance <specify source 1,2,3,4>
- 3.2.6 Purification of extracted substance <specify source 1,2,3,4>
- 3.2.7 Other <free text>

#### 3.3 Manufacture of Active Substance using Biological Processes

- 3.3.1 Fermentation
- 3.3.2 Cell Culture <specify cell type> (e.g. mammalian / bacterial)
- 3.3.3 Isolation / Purification
- 3.3.4 Modification
- 3.3.5 Other <free text>

#### 3.4 Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)

- 3.4.1 Aseptically prepared
- 3.4.2 Terminally sterilised

#### 3.5 General Finishing Steps

- 3.5.1 Physical processing steps <specify> (e.g. drying, milling / micronisation, sieving)
- 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)
- 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
- 3.5.4 Other <free text> (for operations not described above)

#### 3.6 Quality Control Testing

- 3.6.1 Physical / Chemical testing
- 3.6.2 Microbiological testing (excluding sterility testing)
- 3.6.3 Microbiological testing (including sterility testing)
- 3.6.4 Biological Testing
4. OTHER ACTIVITIES- ACTIVE SUBSTANCES

Any restrictions or clarifying remarks related to the scope of this certificate*:

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....../....../...... [date] ..........................................................................................................................................................................................................................................................................................

Name and signature of the authorised person of the Competent Authority of [country]¹

..........................................................................................................................................................................................................................................................................................
..........................................................................................................................................................................................................................................................................................

[name, title, national authority, phone & fax numbers]

(*): delete that which does not apply

¹ The signature, date and contact details should appear on each page of the certificate.
Forms used by regulators

Union Format for a Wholesale Distribution Authorisation (Medicinal Products for Human Use)

<table>
<thead>
<tr>
<th>Title</th>
<th>Union Format for a Wholesale Distribution Authorisation (Medicinal Products for Human Use)</th>
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</thead>
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<td>Reason for revision</td>
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UNION FORMAT FOR A WHOLESALE DISTRIBUTION AUTHORISATION

(MEDICINAL PRODUCTS FOR HUMAN USE)

1. Authorisation number

2. Name of authorisation holder

3. Legally registered address of authorisation holder

4. Address(es) of site(s)
   (All sites should be listed, if not covered by separate authorisations)

5. Scope of authorisation (complete for each site under 4)

6. Legal basis of authorisation

7. Name of responsible officer of the competent authority of the member state granting the wholesaling authorisation

8. Signature

9. Date

10. Annexes attached
    - Annex 1 Scope of wholesale distribution authorisation
    - Annex 2 (Optional) Address(es) of contract wholesale distribution sites and their authorisation number
    - Annex 3 (Optional) Name(s) of responsible person(s)
    - Annex 4 (Optional) Date of Inspection on which authorisation was granted
    - Annex 5 (Optional) Additional provisions based on national requirements
## ANNEX 1

### SCOPE OF WHOLESALE DISTRIBUTION AUTHORISATION

Name and address of the site:

<table>
<thead>
<tr>
<th>1. MEDICINAL PRODUCTS</th>
</tr>
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<tbody>
<tr>
<td>1.1 ☐ with a Marketing Authorisation in EEA country(s)</td>
</tr>
<tr>
<td>1.2 ☐ without a Marketing Authorisation in the EEA and intended for EEA market*</td>
</tr>
<tr>
<td>1.3 ☐ without a Marketing Authorisation in the EEA and intended for exportation</td>
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<table>
<thead>
<tr>
<th>2. AUTHORISED WHOLESALE DISTRIBUTION OPERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 ☐ Procurement</td>
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<tr>
<td>2.2 ☐ Holding</td>
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<td>2.3 ☐ Supply</td>
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<td>2.4 ☐ Export</td>
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<tr>
<td>2.5 ☐ Other activities(s): (please specify)</td>
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<table>
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<th>3. Medicinal products with additional requirements</th>
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<tr>
<td>3.1 ☐ Products according to Art. 83 of 2001/83/EC1</td>
</tr>
<tr>
<td>3.1.1 ☐ Narcotic or psychotropic products</td>
</tr>
<tr>
<td>3.1.2 ☐ Medicinal products derived from blood</td>
</tr>
<tr>
<td>3.1.3 ☐ Immunological medicinal products</td>
</tr>
<tr>
<td>3.1.4 ☐ Radiopharmaceuticals (including radionuclide kits)</td>
</tr>
<tr>
<td>3.2 ☐ Medicinal gases</td>
</tr>
<tr>
<td>3.3 ☐ Cold chain products (requiring low temperature handling)</td>
</tr>
<tr>
<td>3.4 ☐ Other products: (please specify here or make a reference to Annex 5)</td>
</tr>
</tbody>
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Any restrictions or clarifying remarks related to the scope of these wholesaling operations

*Art 5 of Directive 2001/83/EC or Art 83 of Regulation EC/726/2004

---

1 Without prejudice to further authorisations as may be required according to national legislation
ANNEX 2 (Optional)
Address(es) of Contract Wholesale Distribution sites and their authorisation number
.................................................................................................................................
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.................................................................................................................................

ANNEX 3 (Optional)
Name(s) of responsible person(s) ..............................................................................

ANNEX 4 (Optional)
Date of Inspection on which authorisation was granted dd/mm/yyyy
.................................................................................................................................

ANNEX 5 (Optional)
Additional provisions based on national requirements .............................................
Forms used by regulators

**Union Format for a Good Distribution Practice Certificate (Medicinal Products for Human Use)**

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CERTIFICATE OF GDP COMPLIANCE OF A WHOLESALE DISTRIBUTOR

Issued following an inspection in accordance with Art. 111 of Directive 2001/83/EC

The competent authority of ..................................................[Member State] confirms the following:

The wholesale distributor........................................................................................................................................................................
Site address................................................................................................................................................................................................

Has been inspected under the national inspection programme in connection with authorisation number ........................................ in accordance with Art. 77 (1) of Directive 2001/83/EC transposed in the following national legislation:

From the knowledge gained during inspection of this wholesale distributor, the latest of which was conducted on ....../...../...... [date], it is considered that it complies with the Good Distribution Practice requirements laid down in Article 84 of Directive 2001/83/EC.

This certificate reflects the status of the premises at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than five years have elapsed since the date of that inspection. However this period of validity may be reduced using regulatory risk management principles, by an entry in the Restrictions or Clarifying Remarks field.

This certificate is valid only when presented with all pages.

The authenticity of this certificate may be verified in the Union database. If it does not appear please contact the issuing authority.

Any restrictions or clarifying remarks related to the scope of this certificate:

...............................................................

....../....../...... [Date] Name and signature of the authorised person of the Competent Authority of [country]¹

...............................................................

[name, title, national authority, phone, email in case of enquiries]

Details of the authorisation can be found in the Union Database.

1 The signature, date and contact details should appear on each page of the certificate.
Forms used by regulators

Union Format for a Good Distribution Practice Certificate for Active Substances to be used as Starting Materials in Medicinal Products for Human Use

<table>
<thead>
<tr>
<th>Title</th>
<th>Union Format for a GDP Certificate for Active Substances</th>
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<td>Date of adoption</td>
<td>May 2012</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 2 January 2013</td>
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</table>
CERTIFICATE OF GDP COMPLIANCE OF A DISTRIBUTOR OF ACTIVE SUBSTANCES FOR USE AS STARTING MATERIALS IN MEDICINAL PRODUCTS FOR HUMAN USE

Issued following an inspection in accordance with Art. 111 of Directive 2001/83/EC

The competent authority of ………………………………………………………………………………….. [Member State] confirms the following:

The active substance distributor……………………………………………………………………………………………………………………………………….
Site address……………………………………………………………………………………………………………………………………………………….
………………………………………………………………………………………………………………………………………………………….
has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation:
………………………………………………………………………………………………………………………………………………………….
and in connection with registration no*……………………………………………………

From the knowledge gained during inspection of this active substance distributor, the latest of which was conducted on …../……/…… [Date], it is considered that it complies with the principles of good distribution practice for active substances referred to in article 47 of Directive 2001/83/EC

This certificate reflects the status of the site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than five years have elapsed since the date of that inspection. However this period of validity may be reduced using regulatory risk management principles, by an entry in the Restrictions or Clarifying Remarks field.

The authenticity of this certificate may be verified in the Union database. If it does not appear please contact the issuing authority.

Any restrictions or clarifying remarks related to the scope of this certificate:

..............................................................................................................................................................................................
..............................................................................................................................................................................................
............./........../…… [date] Name and signature of the authorised person of the Competent Authority of [country]1
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..............................................................................................................................................................................................
..............................................................................................................................................................................................
[.../.../... [date] [name, title, name of authority, phone, email in case of enquiries]

*Delete where not applicable

1 The signature, date and contact details should appear on each page of the certificate.

Compilation of Community Procedures on Inspections and Exchange of Information

EMA/INS/GMP/321252/2012 Page 140/177
Forms used by regulators

Statement of Non-Compliance with GMP

<table>
<thead>
<tr>
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STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer

Part 1

Issued following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC, Art. 80(7) of Directive 2001/82/EC or Art. 15 of Directive 2001/20/EC.*

The competent authority of.................................................................[Member State] confirms the following:

The manufacturer ................................................................................................................................................

Site address ..........................................................................................................................................................
### Part 2

- **Human Medicinal Products**
- **Veterinary Medicinal Products**
- **Human Investigational Medicinal Products**

#### 1 NON-COMPLIANT MANUFACTURING OPERATIONS - MEDICINAL PRODUCTS *

##### 1.1 Sterile Products

1.1.1 *Aseptically prepared (processing operations for the following dosage forms)*
- 1.1.1.1 Large volume liquids
- 1.1.1.2 Lyophilisates
- 1.1.1.3 Semi-solids
- 1.1.1.4 Small volume liquids
- 1.1.1.5 Solids and implants
- 1.1.1.6 Other aseptically prepared products <free text>

1.1.2 *Terminally sterilised (processing operations for the following dosage forms)*
- 1.1.2.1 Large volume liquids
- 1.1.2.2 Semi-solids
- 1.1.2.3 Small volume liquids
- 1.1.2.4 Solids and implants
- 1.1.2.5 Other terminally sterilised prepared products <free text>

1.1.3 *Batch certification*

##### 1.2 Non-sterile Products

1.2.1 *Non-sterile products (processing operations for the following dosage forms)*
- 1.2.1.1 Capsules, hard shell
- 1.2.1.2 Capsules, soft shell
- 1.2.1.3 Chewing gums
- 1.2.1.4 Impregnated matrices
- 1.2.1.5 Liquids for external use
- 1.2.1.6 Liquids for internal use
- 1.2.1.7 Medicinal gases
- 1.2.1.8 Other solid dosage forms
- 1.2.1.9 Pressurised preparations
- 1.2.1.10 Radionuclide generators
- 1.2.1.11 Semi-solids
- 1.2.1.12 Suppositories
- 1.2.1.13 Tablets
- 1.2.1.14 Transdermal patches
- 1.2.1.15 Intraruminal devices
- 1.2.1.16 Veterinary premixes
- 1.2.1.17 Other non-sterile medicinal product <free text>

1.2.2 *Batch certification*

##### 1.3 Biological medicinal products

1.3.1 *Biological medicinal products*
- 1.3.1.1 Blood products
- 1.3.1.2 Immunological products
- 1.3.1.3 Cell therapy products
- 1.3.1.4 Gene therapy products
- 1.3.1.5 Biotechnology products
- 1.3.1.6 Human or animal extracted products
- 1.3.1.7 Tissue engineered products
- 1.3.1.8 Other biological medicinal products <free text>
### 1.3.2 Batch certification (list of product types)
- 1.3.2.1 Blood products
- 1.3.2.2 Immunological products
- 1.3.2.3 Cell therapy products
- 1.3.2.4 Gene therapy products
- 1.3.2.5 Biotechnology products
- 1.3.2.6 Human or animal extracted products
- 1.3.2.7 Tissue engineered products
- 1.3.2.8 Other biological medicinal products <free text>

### 1.4 Other products or manufacturing activity

#### 1.4.1 Manufacture of:
- 1.4.1.1 Herbal products
- 1.4.1.2 Homoeopathic products
- 1.4.1.3 Other <free text>

#### 1.4.2 Sterilisation of active substances/exipients/finished product:
- 1.4.2.1 Filtration
- 1.4.2.2 Dry heat
- 1.4.2.3 Moist heat
- 1.4.2.4 Chemical
- 1.4.2.5 Gamma irradiation
- 1.4.2.6 Electron beam

#### 1.4.3 Others <free text>

### 1.5 Packaging

#### 1.5.1 Primary packing
- 1.5.1.1 Capsules, hard shell
- 1.5.1.2 Capsules, soft shell
- 1.5.1.3 Chewing gums
- 1.5.1.4 Impregnated matrices
- 1.5.1.5 Liquids for external use
- 1.5.1.6 Liquids for internal use
- 1.5.1.7 Medicinal gases
- 1.5.1.8 Other solid dosage forms
- 1.5.1.9 Pressurised preparations
- 1.5.1.10 Radioisotope generators
- 1.5.1.11 Semi-solids
- 1.5.1.12 Suppositories
- 1.5.1.13 Tablets
- 1.5.1.14 Transdermal patches
- 1.5.1.15 Intraruminal devices
- 1.5.1.16 Veterinary premixes
- 1.5.1.17 Other non-sterile medicinal products <free text>

#### 1.5.2 Secondary packing

### 1.6 Quality control testing

#### 1.6.1 Microbiological: sterility

#### 1.6.2 Microbiological: non-sterility

#### 1.6.3 Chemical/Physical

#### 1.6.4 Biological

### 2 NON-COMPLIANT IMPORTATION OPERATIONS*

#### 2.1 Quality control testing of imported medicinal products

- 2.1.1 Microbiological: sterility
- 2.1.2 Microbiological: non-sterility
- 2.1.3 Chemical/Physical
### 2.1.4 Biological

#### 2.2 Batch certification of imported medicinal products

##### 2.2.1 Sterile Products
- 2.2.1.1 Aseptically prepared
- 2.2.1.2 Terminally sterilised

##### 2.2.2 Non-sterile products

##### 2.2.3 Biological medicinal products
- 2.2.3.1 Blood products
- 2.2.3.2 Immunological products
- 2.2.3.3 Cell therapy products
- 2.2.3.4 Gene therapy products
- 2.2.3.5 Biotechnology products
- 2.2.3.6 Human or animal extracted products
- 2.2.3.7 Tissue engineered products
- 2.2.3.8 Other biological medicinal products <free text>

##### 2.3 Other importation activities

- 2.3.1 Site of physical importation
- 2.3.2 Importation of intermediate which undergoes further processing
- 2.3.3 Other <free text>

Any restrictions or clarifying remarks related to the scope of this statement*:

..................................................................................................................................................
..................................................................................................................................................
..................................................................................................................................................

### 3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance(s):
### 3.1 Manufacture of Active Substance by Chemical Synthesis

- 3.1.1 Manufacture of active substance intermediates
- 3.1.2 Manufacture of crude active substance
- 3.1.3 Salt formation / Purification steps: <free text> (e.g. crystallisation)
- 3.1.4 Other <free text>

### 3.2 Extraction of Active Substance from Natural Sources

- 3.2.1 Extraction of substance from plant source
- 3.2.2 Extraction of substance from animal source
- 3.2.3 Extraction of substance from human source
- 3.2.4 Extraction of substance from mineral source
- 3.2.5 Modification of extracted substance <specify source 1,2,3,4>
- 3.2.6 Purification of extracted substance <specify source 1,2,3,4>
- 3.2.7 Other <free text>

### 3.3 Manufacture of Active Substance using Biological Processes

- 3.3.1 Fermentation
- 3.3.2 Cell Culture <specify cell type> (e.g. mammalian / bacterial)
- 3.3.3 Isolation / Purification
- 3.3.4 Modification
- 3.3.5 Other <free text>

### 3.4 Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)

- 3.4.1 Aseptically prepared
- 3.4.2 Terminally sterilised

### 3.5 General Finishing Steps

- 3.5.1 Physical processing steps <specify> (e.g. drying, milling / micronisation, sieving)
- 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)
- 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
- 3.5.4 Other <free text> (for operations not described above)

### 3.6 Quality Control Testing

- 3.6.1 Physical / Chemical testing
- 3.6.2 Microbiological testing (excluding sterility testing)
- 3.6.3 Microbiological testing (including sterility testing)
- 3.6.4 Biological Testing

### 4. OTHER ACTIVITIES- ACTIVE SUBSTANCES

<free text>
Any restrictions or clarifying remarks related to the scope of this statement*:

...........................................................................................................................................
...........................................................................................................................................
## Part 3

### 1. Nature of non-compliance

<free text:>

### 2. Action taken/proposed by the NCA

- **Suspension/variation/revocation** of the manufacturing authorisation No. .................. in full/in part*

  <free text:>

- **Restriction of current valid GMP certificate** No. ..................................................

  <free text:>

- **Suspension/revocation/requested variation/ refusal to grant** * of Marketing Authorisation(s)

  <free text:>

- **Recall of batches already released** (separate Rapid Alert to follow)

  <free text:>

- **Prohibition of supply**

  <free text:>

- **Suspension or voiding of CEP** (action to be taken by EDQM)

  <free text:>

- **Suspension of clinical trials**

  <free text:>

- **Others** <free text:>

  <free text:>

### 3. Additional comments

<free text:>

<free text:>
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<th>Dial in no.</th>
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<table>
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<th>Product</th>
<th>Dosage Form</th>
<th>Reference Member State, National or EMEA</th>
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<tr>
<td>Human medicinal product(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterinary medicinal product(s)</td>
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<tr>
<td>Investigational medicinal product(s)</td>
<td>EudraCT nos.</td>
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<td></td>
</tr>
</tbody>
</table>

....../....../...... [date]

Name and signature of the authorised person of the Competent Authority of [country]

[Name, title, national authority, phone & fax numbers in case of enquiries]

---

1 The signature, date and contact details should appear on each page of the non-compliance document.
Forms used by regulators

Notification of Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations

<table>
<thead>
<tr>
<th>Title</th>
<th>Notification of Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations</th>
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<td>Date of adoption</td>
<td>May 2012</td>
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<tr>
<td>Date of entry into force</td>
<td>By end November 2012</td>
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<td>Supersedes</td>
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<td>Reason for revision</td>
<td>Not Applicable, new guideline</td>
</tr>
<tr>
<td>Notes</td>
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</table>
NOTIFICATION OF SERIOUS GMP NON-COMPLIENCE
INFORMATION ORIGINATING FROM THIRD COUNTRY
AUTHORITIES OR INTERNATIONAL ORGANIZATIONS

Exchange of information between National Competent Authorities (NCAs) of the EEA
following notification of serious GMP non-compliance at a manufacturer.

Part 1

Issued by the competent authority of [Member State] following notification from a
third country authority or international organisation in accordance with reference to CoCP here.

[third country authority / International organisation name] reports the following:

The manufacturer

Site address

DUNS Number (if known)

Site contact name, title, email, phone and fax
number

Third country authority / international organisation contact name, title, email, phone and fax
number

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted
on [date], or from verified information it is considered that it does not comply with the
Good Manufacturing Practice requirements referred to in the principles and guidelines of Good
Manufacturing Practice laid down in [third country / international GMP
standards or regulations used for assessment], relating to medicinal products/ active substances/
excipients*
## Part 2

- Human Medicinal Products*
- Veterinary Medicinal Products*
- Human Investigational Medicinal Products*

### 1 NON-COMPLIANT MANUFACTURING OPERATIONS – MEDICINAL PRODUCTS *

#### 1.1 Sterile Products

1.1.4 Aseptically prepared (processing operations for the following dosage forms)

- 1.1.4.7 Large volume liquids
- 1.1.4.8 Lyophilisates
- 1.1.4.9 Semi-solids
- 1.1.4.10 Small volume liquids
- 1.1.4.11 Solids and implants
- 1.1.4.12 Other aseptically prepared products <free text>

1.1.5 Terminally sterilised (processing operations for the following dosage forms)

- 1.1.5.6 Large volume liquids
- 1.1.5.7 Semi-solids
- 1.1.5.8 Small volume liquids
- 1.1.5.9 Solids and implants
- 1.1.5.10 Other terminally sterilised prepared products <free text>

1.1.6 Batch certification

#### 1.2 Non-sterile products

1.2.3 Non-sterile products (processing operations for the following dosage forms)

- 1.2.3.1 Capsules, hard shell
- 1.2.3.2 Capsules, soft shell
- 1.2.3.3 Chewing gums
- 1.2.3.4 Impregnated matrices
- 1.2.3.5 Liquids for external use
- 1.2.3.6 Liquids for internal use
- 1.2.3.7 Medicinal gases
- 1.2.3.8 Other solid dosage forms
- 1.2.3.9 Pressurised preparations
- 1.2.3.10 Radionuclide generators
- 1.2.3.11 Semi-solids
- 1.2.3.12 Suppositories
- 1.2.3.13 Tablets
- 1.2.3.14 Transdermal patches
- 1.2.3.15 Intraruminal devices
- 1.2.3.16 Veterinary premixes
- 1.2.3.17 Other non-sterile medicinal product <free text>

1.2.4 Batch certification

#### 1.3 Biological medicinal products
# Biological medicinal products

- 1.3.3.1 Blood products
- 1.3.3.2 Immunological products
- 1.3.3.3 Cell therapy products
- 1.3.3.4 Gene therapy products
- 1.3.3.5 Biotechnology products
- 1.3.3.6 Human or animal extracted products
- 1.3.3.7 Tissue engineered products
- 1.3.3.8 Other biological medicinal products <free text>

# Batch certification (list of product types)

- 1.3.4.1 Blood products
- 1.3.4.2 Immunological products
- 1.3.4.3 Cell therapy products
- 1.3.4.4 Gene therapy products
- 1.3.4.5 Biotechnology products
- 1.3.4.6 Human or animal extracted products
- 1.3.4.7 Tissue engineered products
- 1.3.4.8 Other biological medicinal products <free text>

# Other products or manufacturing activity

## Manufacture of:

- 1.4.3.1 Herbal products
- 1.4.3.2 Homoeopathic products
- 1.4.1.3 Other <free text>

## Sterilisation of active substances/excipients/finished product:

- 1.4.4.1 Filtration
- 1.4.4.2 Dry heat
- 1.4.4.3 Moist heat
- 1.4.4.4 Chemical
- 1.4.4.5 Gamma irradiation
- 1.4.4.6 Electron beam

## Others <free text>

# Packaging

## Primary packing

- 1.5.1.18 Capsules, hard shell
- 1.5.1.19 Capsules, soft shell
- 1.5.1.20 Chewing gums
- 1.5.1.21 Impregnated matrices
- 1.5.1.22 Liquids for external use
- 1.5.1.23 Liquids for internal use
- 1.5.1.24 Medicinal gases
- 1.5.1.25 Other solid dosage forms
- 1.5.1.26 Pressurised preparations
- 1.5.1.27 Radionuclide generators
- 1.5.1.28 Semi-solids
- 1.5.1.29 Suppositories
- 1.5.1.30 Tablets
- 1.5.1.31 Transdermal patches
- 1.5.1.32 Intraruminal devices
- 1.5.1.33 Veterinary premixes
- 1.5.1.34 Other non-sterile medicinal products <free text>

## Secondary packing

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Compilation of Community Procedures on Inspections and Exchange of Information

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<table>
<thead>
<tr>
<th>1.6</th>
<th>Quality control testing</th>
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<tbody>
<tr>
<td>1.6.5</td>
<td>Microbiological: sterility</td>
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<td>Microbiological: non-sterility</td>
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<tr>
<td>1.6.7</td>
<td>Chemical/Physical</td>
</tr>
<tr>
<td>1.6.8</td>
<td>Biological</td>
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</table>
## 2 NON-COMPLIANT IMPORTATION OPERATIONS*

### 2.1 Quality control testing of imported medicinal products

<table>
<thead>
<tr>
<th>2.1.5</th>
<th>Microbiological: sterility</th>
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<tbody>
<tr>
<td>2.1.6</td>
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<tr>
<td>2.1.7</td>
<td>Chemical/Physical</td>
</tr>
<tr>
<td>2.1.8</td>
<td>Biological</td>
</tr>
</tbody>
</table>

### 2.2 Batch certification of imported medicinal products

#### 2.2.4 Sterile Products

- 2.2.4.1 Aseptically prepared
- 2.2.4.2 Terminally sterilised

#### 2.2.5 Non-sterile products

#### 2.2.6 Biological medicinal products

- 2.2.3.9 Blood products
- 2.2.3.10 Immunological products
- 2.2.3.11 Cell therapy products
- 2.2.3.12 Gene therapy products
- 2.2.3.13 Biotechnology products
- 2.2.3.14 Human or animal extracted products
- 2.2.3.15 Tissue engineered products
- 2.2.3.16 Other biological medicinal products <free text>

### 2.3 Other importation activities

#### 2.3.1 Site of physical importation

#### 2.3.2 Importation of intermediate which undergoes further processing

#### 2.3.3 Other <free text>

Any restrictions or clarifying remarks related to the scope of this notification*:
### 3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

#### Active Substance(s):

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<tr>
<th>Section</th>
<th>Description</th>
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<tbody>
<tr>
<td>3.1</td>
<td><strong>Manufacture of Active Substance by Chemical Synthesis</strong></td>
</tr>
<tr>
<td>3.1.1</td>
<td>Manufacture of active substance intermediates</td>
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<tr>
<td>3.1.2</td>
<td>Manufacture of crude active substance</td>
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<td>Salt formation / Purification steps: &lt;free text&gt; (e.g. crystallisation)</td>
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<td>Other &lt;free text&gt;</td>
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<tbody>
<tr>
<td>3.2</td>
<td><strong>Extraction of Active Substance from Natural Sources</strong></td>
</tr>
<tr>
<td>3.2.1</td>
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<td>3.2.2</td>
<td>Extraction of substance from animal source</td>
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<tr>
<td>3.2.3</td>
<td>Extraction of substance from human source</td>
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<tr>
<td>3.2.4</td>
<td>Extraction of substance from mineral source</td>
</tr>
<tr>
<td>3.2.5</td>
<td>Modification of extracted substance &lt;specify source 1,2,3,4&gt;</td>
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<td>3.2.6</td>
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<tbody>
<tr>
<td>3.3</td>
<td><strong>Manufacture of Active Substance using Biological Processes</strong></td>
</tr>
<tr>
<td>3.3.1</td>
<td>Fermentation</td>
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<td>3.3.2</td>
<td>Cell Culture &lt;specify cell type&gt; (e.g. mammalian / bacterial)</td>
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<tr>
<td>3.3.3</td>
<td>Isolation / Purification</td>
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<td>Modification</td>
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<tr>
<td>3.4</td>
<td><strong>Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)</strong></td>
</tr>
<tr>
<td>3.4.1</td>
<td>Aseptically prepared</td>
</tr>
<tr>
<td>3.4.2</td>
<td>Terminally sterilised</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td><strong>General Finishing Steps</strong></td>
</tr>
<tr>
<td>3.5.1</td>
<td>Physical processing steps &lt;specify&gt; (e.g. drying, milling / micronisation, sieving)</td>
</tr>
<tr>
<td>3.5.2</td>
<td>Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</td>
</tr>
<tr>
<td>3.5.3</td>
<td>Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</td>
</tr>
<tr>
<td>3.5.4</td>
<td>Other &lt;free text&gt; (for operations not described above)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td><strong>Quality Control Testing</strong></td>
</tr>
<tr>
<td>3.6.1</td>
<td>Physical / Chemical testing</td>
</tr>
<tr>
<td>3.6.2</td>
<td>Microbiological testing (excluding sterility testing)</td>
</tr>
<tr>
<td>3.6.3</td>
<td>Microbiological testing (including sterility testing)</td>
</tr>
<tr>
<td>3.6.4</td>
<td>Biological Testing</td>
</tr>
</tbody>
</table>
Part 3

1. Nature of non-compliance (check all relevant boxes)

<table>
<thead>
<tr>
<th>Analytical validation</th>
<th>Housekeeping - cleanliness, tidiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch release procedures</td>
<td>In-process controls - control and monitoring of production operations</td>
</tr>
<tr>
<td>Calibration of measuring and test equipment</td>
<td>Intermediate and bulk product testing</td>
</tr>
<tr>
<td>Calibration of reference materials and reagents</td>
<td>Investigation of anomalies</td>
</tr>
<tr>
<td>Cleaning validation</td>
<td>Line clearance, segregation and potential for mix-up</td>
</tr>
<tr>
<td>Complaints and product recall</td>
<td>Personnel issues: Duties of key personnel</td>
</tr>
<tr>
<td>Computerised systems - documentation and control</td>
<td>Personnel issues: Hygiene/Clothing</td>
</tr>
<tr>
<td>Computerised systems - validation</td>
<td>Personnel issues: Training</td>
</tr>
<tr>
<td>Contamination, chemical/physical - potential for</td>
<td>Process validation</td>
</tr>
<tr>
<td>Contamination, microbiological - potential for</td>
<td>Production planning and scheduling</td>
</tr>
<tr>
<td>Design and maintenance of equipment</td>
<td>Regulatory issues: Non-compliance with manufacturing authorisation</td>
</tr>
<tr>
<td>Design and maintenance of premises</td>
<td>Regulatory issues: Non-compliance with marketing authorisation</td>
</tr>
<tr>
<td>Documentation - manufacturing</td>
<td>Regulatory issues: Unauthorised activities</td>
</tr>
<tr>
<td>Documentation - quality system elements/procedures</td>
<td>Sampling - procedures and facilities</td>
</tr>
<tr>
<td>Equipment qualification</td>
<td>Sterility Assurance</td>
</tr>
<tr>
<td>Finished product testing</td>
<td>Supplier and contractor audit and technical agreements</td>
</tr>
<tr>
<td>Handling and control of packaging components</td>
<td>Warehousing and distribution activities</td>
</tr>
</tbody>
</table>
2. **Action taken/proposed** by the third country authority or International organisation:

- Suspension, variation, revocation of the manufacturing site approval in full or in part
- Withdrawal, of current valid GMP certificate / statement
- **Suspension, Revocation or Requested Variation** of product registrations
- Recall of batches already released
- Prohibition of supply
- Suspension of clinical trials
- Others <free text>

3. Additional comments
<table>
<thead>
<tr>
<th>Teleconference Date</th>
<th>Teleconference Time (GMT)</th>
<th>Dial in no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU Products manufactured at site, if known</td>
<td>Product</td>
<td>Dosage Form</td>
</tr>
<tr>
<td>Human medicinal product(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterinary medicinal product(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational medicinal product(s)</td>
<td>EudraCT nos.</td>
<td></td>
</tr>
</tbody>
</table>

Name of the authorised person of the Competent Authority of .......................... [Member State]

.................................................................
[Name, title, national authority, email, phone & fax numbers in case of enquiries]

...../....../....... [Date]

(*): delete that which does not apply
Forms used by regulators

Statement of Non-compliance with Good Distribution Practice
(Medicinal Products for Human use)

<table>
<thead>
<tr>
<th>Title</th>
<th>Statement of Non-Compliance with Good Distribution Practice Medicinal Products for Human Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>May 2012</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 2 January 2013</td>
</tr>
<tr>
<td>Supersedes</td>
<td>New</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>New</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
STATEMENT OF NON-COMPLIANCE WITH GDP
MEDICINAL PRODUCTS FOR HUMAN USE

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GDP non-compliance at a wholesale distributor

Part 1

Issued following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC as amended.

The competent authority of..................................................[Member State] confirms the following:

The wholesale distributor.............................................................Authorisation number..........................................................
Site address...............................................................................

From the knowledge gained during inspection of this wholesaler distributor, the latest of which was conducted on .....[date], it is considered that it does not comply with the Good Distribution Practice requirements referred to in Article 84 of Directive 2001/83/EC.

Part 2

Wholesale distribution activity affected: <free text>

Part 3

1. Nature of non-compliance: <free text>

2. Action taken/proposed by the NCA: <free text>

3. Additional comments: <free text>

Teleconference Date: Teleconference Time (CET): Dial in no.: 

.....[date] Name and signature of the authorised person of the Competent Authority of [country]¹
...........................................................................................................
...........................................................................................................
...........................................................................................................
...........................................................................................................

¹ The signature, date and contact details should appear on each page of the statement.

Page 1 of <insert number of pages>
Forms used by regulators

Statement of Non-compliance with Good Distribution Practice of a Distributor of Active Substances for Use as Starting Materials in Medicinal Products for Human Use

<table>
<thead>
<tr>
<th>Title</th>
<th>Statement of Non-compliance with Good Distribution Practice of a Distributor of Active Substances for Use as Starting Materials in Medicinal Products for Human Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>May 2012</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 2 January 2013</td>
</tr>
<tr>
<td>Supersedes</td>
<td>New</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>New</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
STATEMENT OF NON-COMPLIANCE WITH GDP OF A DISTRIBUTOR OF ACTIVE SUBSTANCES FOR USE AS STARTING MATERIALS IN MEDICINAL PRODUCTS FOR HUMAN USE

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GDP non-compliance at an active substance distributor

Part 1

Issued following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC as amended.

The competent authority of……………………………………………….[Member State] confirms the following:

The active substance distributor……………………………………………………………………………………………………………..

Site address …………………………………………………………………………………………………………………………………………..

From the knowledge gained during inspection of this active substance distributor, the latest of which was conducted on …/…/… [date], it is considered that it does not comply with the Good Distribution Practice for active substances referred to in Article 47 of Directive 2001/83/EC.

Part 2

☐ All registered active substances distributed are affected

☐ Specify which Active Substances are affected : <free text >

Part 3

4. Nature of non-compliance: <free text >

5. Action taken/proposed by the NCA: <free text >

6. Additional comments: <free text >

Teleconference Date: Teleconference Time (CET): Dial in no.:

…/…/… [date]

Name and signature of the authorised person of the Competent Authority of [country]

………………………………………………………………………………………………………………………………………………..

[Name, title, name of authority, phone, email in case of enquiries]

1 The signature, date and contact details should appear on each page of this statement.
Forms used by regulators

Request Form for the Exchange of Information on Marketing Authorisation Holders or Manufacturing Authorisation Holders between the Competent Authorities in the EEA

<table>
<thead>
<tr>
<th>Title</th>
<th>Request Form for the Exchange of Information on Marketing Authorisation Holders or Manufacturing Authorisation Holders between the Competent Authorities in the EEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>May 2012</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 2 January 2013</td>
</tr>
<tr>
<td>Supersedes</td>
<td>New</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>New</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
Request Form for the Exchange of Information on Marketing Authorisation Holders or Manufacturing Authorisation Holders between the Competent Authorities in the EEA

The templates below were developed in order to facilitate exchange of information between the competent authorities in EEA where there are no established procedures or systems (e.g. EudraGMP) for the exchange of information.

<table>
<thead>
<tr>
<th>Reference no.:</th>
<th>No. of pages/No. of attachments:</th>
<th>Date:</th>
</tr>
</thead>
</table>

**Requesting Competent Authority**

<table>
<thead>
<tr>
<th>Competent Authority/ Country</th>
<th>Address/phone/fax</th>
<th>Contact Person</th>
<th>Email of Contact Person</th>
</tr>
</thead>
</table>

**Recipient Competent Authority**

<table>
<thead>
<tr>
<th>Competent Authority/ Country</th>
<th>Address/phone/fax</th>
<th>Contact Person</th>
<th>Email of Contact Person</th>
</tr>
</thead>
</table>

**Request for Exchange of Information on** [complete as appropriate]

<table>
<thead>
<tr>
<th>MAH- Address/phone/fax/Email</th>
<th>QPPV/ PSMF site – Address/phone</th>
<th>Medicinal Product/dosage form/strength/INN/MA</th>
<th>Manufacturer- Address/phone/fax/Email</th>
<th>Information requested</th>
</tr>
</thead>
</table>
Reply Form in Response to a Request for the Exchange of Information on Marketing Authorisation Holders or Manufacturing Authorisation Holders between the Competent Authorities in the EEA

As requested by the competent authority of ………………………………………………………………………on …/……/……
(Original Ref. no. :……………),
the competent authority of…………………………………………………………………………………………………………..
confirms the following information:
The MAH and/ or QPPV/PSMF or the Manufacturer (delete as appropriate)………………………………………………
…………………………………………………………………………………………………………………………………………………..
(Medicinal Product/dosage form/strength/INN/MA)………………………………………………………………………………
Address………………………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………………………………..
…………………………………………………………………………………………………………………………………………………..
…………………………………………………………………………………………………………………………………………………..
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…………………………………………………………………………………………………………………………………………………..
…………………………………………………………………………………………………………………………………………………..
…………………………………………………………………………………………………………………………………………………..
…………………………………………………………………………………………………………………………………………………..
Name and signature of a responsible officer of the reporting competent authority:
…………………………………………………………………………………………………………………………………………………..
Date:………………
Registration of Manufacturer, Importer or Distributor of Active Substance (used in Medicinal Products for Human Use)

**Union Format for Registration of Manufacturer, Importer or Distributor of Active Substance (used in Medicinal Products for Human Use)**

<table>
<thead>
<tr>
<th>Title</th>
<th>Union Format for Registration of Manufacturer, Importer or Distributor for Active Substance (used in Medicinal Products for Human Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td>May 2012</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>By 2 January 2013</td>
</tr>
<tr>
<td>Supersedes</td>
<td>New</td>
</tr>
<tr>
<td>Reason for revision</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
Union Format for Registration\(^1\) of Manufacturer, Importer or Distributor of Active Substances

1. Registration number

2. Name or corporate name of registrant

3. Permanent or Legal address of registrant

4. Address(es) of site(s) where registered activities take place
   All relevant sites should be listed if not covered by separate registrations

5. National legal basis of registration

6. Name of responsible officer of the competent authority of the member state validating the registration\(^2\)

7. Signature\(^2\)

8. Date

This registration form is valid only when presented with all pages. The authenticity of this registration form may be verified in the Union database or with the validating authority.

The registration holder referred to in section 2 shall communicate annually to the competent authority an inventory of the changes which have taken place as regards the information provided in this registration form. Any changes that may have an impact on the quality or safety of the listed active substances must be notified immediately.

---

\(^1\) Without prejudice to any further national legislative requirements

\(^2\) Optional

Registration No:

Page # of #
**SCOPE OF REGISTRATION**
Name and address of the site:

### 1. MANUFACTURING OPERATIONS

<table>
<thead>
<tr>
<th>Active Substance(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Manufacture of Active Substance by Chemical Synthesis</td>
</tr>
<tr>
<td>1. Manufacture of active substance intermediates</td>
</tr>
<tr>
<td>2. Manufacture of crude active substance</td>
</tr>
<tr>
<td>3. Salt formation / Purification steps: <em>(free text)</em> <em>(e.g. crystallisation)</em></td>
</tr>
<tr>
<td>4. Other <em>(free text)</em></td>
</tr>
<tr>
<td><strong>B</strong> Extraction of Active Substance from Natural Sources</td>
</tr>
<tr>
<td>1. Extraction of substance from plant source</td>
</tr>
<tr>
<td>2. Extraction of substance from animal source</td>
</tr>
<tr>
<td>3. Extraction of substance from human source</td>
</tr>
<tr>
<td>4. Extraction of substance from mineral source</td>
</tr>
<tr>
<td>5. Modification of extracted substance <em>(specify source 1,2,3,4)</em></td>
</tr>
<tr>
<td>6. Purification of extracted substance <em>(specify source 1,2,3,4)</em></td>
</tr>
<tr>
<td>7. Other <em>(free text)</em></td>
</tr>
<tr>
<td><strong>C</strong> Manufacture of Active Substance using Biological Processes</td>
</tr>
<tr>
<td>1. Fermentation</td>
</tr>
<tr>
<td>2. Cell Culture <em>(specify cell type)</em> <em>(e.g. mammalian / bacterial)</em></td>
</tr>
<tr>
<td>3. Isolation / Purification</td>
</tr>
<tr>
<td>4. Modification</td>
</tr>
<tr>
<td>5. Other <em>(free text)</em></td>
</tr>
<tr>
<td><strong>D</strong> Manufacture of sterile active substance <em>(note Parts A, B &amp; C, to be completed as applicable)</em></td>
</tr>
<tr>
<td>1. Aseptically prepared</td>
</tr>
<tr>
<td>2. Terminally sterilised</td>
</tr>
<tr>
<td><strong>E</strong> General Finishing Steps</td>
</tr>
<tr>
<td>1. Physical processing steps <em>(specify)</em> <em>(e.g. drying, milling / micronisation, sieving)</em></td>
</tr>
<tr>
<td>2. Primary Packaging <em>(enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</em></td>
</tr>
<tr>
<td>3. Secondary Packaging <em>(placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</em></td>
</tr>
<tr>
<td>4. Other <em>(free text)</em> <em>(for operations not described above)</em></td>
</tr>
</tbody>
</table>
### Quality Control Testing

*This section should be completed only if any parts of sections A, B, C, D, E are completed*

1. Physical / Chemical testing
2. Microbiological testing (excluding sterility testing)
3. Microbiological testing (including sterility testing)
4. Biological Testing

### 2. IMPORTATION AND DISTRIBUTION OPERATIONS

#### A Importation

*(list all imported active substances together with details of the relevant manufacturers, and where applicable, distributors)*

<table>
<thead>
<tr>
<th>Active substance</th>
<th>3rd country manufacturer (name &amp; address)</th>
<th>Distributor (name &amp; address)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### B Distribution

*Active substance(s) (list all active substances for which distribution operations apply)*

Any restrictions or clarifying remarks related to the scope of these registered operations

..............................................................................................................................................................................................................................................................................................................................

..............................................................................................................................................................................................................................................................................................................................................................................................................................................................

Name of responsible officer of the competent authority of the member state validating the registration

Signature

---

1 Optional

Registration No:  
Page # of #
Procedures Related to Centralised Procedures

Co-ordinating GMP Inspections for Centrally Authorised Products

Table of contents:
- Introduction
- Scope
- Legal Basis
- General Procedure for GMP Inspection
- Pre-submission Notification by the Applicant for a Marketing Authorisation
- Designation of an Inspection Team and Preparation for the Inspection
- Contacts with the Applicant and the Manufacturer(s) to be Inspected
- Submission of the Final Report to the Rapporteur and the EMA

<table>
<thead>
<tr>
<th>Title</th>
<th>Coordinating GMP Inspections for Centrally Authorised Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of adoption</td>
<td></td>
</tr>
<tr>
<td>Date of entry into force</td>
<td></td>
</tr>
<tr>
<td>Supersedes</td>
<td>Procedure for Co-ordinating Foreign and Community Pre-Authorisation Inspections during the Assessment of Applications published January 2001</td>
</tr>
<tr>
<td>Reason for revision</td>
<td>Reviewed following the harmonisation of the Community report format for centrally and non-centrally co-ordinated inspections. Scope extended to include routine re-inspections</td>
</tr>
<tr>
<td>Notes</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Co-ordinating GMP Inspections for Centrally Authorised Products

1. Introduction

This guideline should be read in conjunction with the terms of the standard contract between the European Medicines Agency (EMA) and the Competent Authorities of the EU Member States.

2. Scope

For GMP inspections carried out by competent authorities of the Member States of the European Economic Area (EEA) at the request of the EMA.

3. Legal Basis

In order to complete the assessment of applications for marketing authorisations under the centralised system the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP) may request that an inspection is carried out of the manufacturing site for a medicinal product in accordance with Articles 8 (2) and 33 (2) respectively of Regulation 726/2004 of the European Parliament and the Council.

Repeated (routine re-inspections) may also be requested according to the provisions of Articles 19(3) and 44(3) of the same Regulation.

4. General Procedure for GMP Inspection

4.1 Inspections coordinated by the EMA are managed using the Corporate GXP application.

4.2 Inspection reports will be prepared by the inspectors of the supervisory authority of the Member State for all inspections requested by either the CHMP or CVMP under the obligations of Articles 18 or 43 of Regulation 726/2004.

(Note: Should a supervisory authority not be able to inspect in a third country, another competent authority may be requested to carry out the inspection following the Community Procedure on delegation of responsibilities)

4.3 The Inspectors of the supervisory authority may be assisted in the preparation of the report by experts appointed by either the CHMP or CVMP to take part in the inspection.

4.4 The EMA requires the inspection report to be in English.

4.5 The content and format of the report should be that described in the Compilation of Community procedures.

4.6 The report should address any questions raised by the Rapporteur/Co-Rapporteur relating to the assessment of the manufacturing activities and/or control procedures or any other specific issues identified by the CHMP or the CVMP and/or the EMA (e.g. reported problems, quality defects) as relevant.
4.7 The inspection report should be finalised and sent to the EMA (uploaded to the Corporate GXP application and signed by all inspectors) within the timelines identified in the relevant inspection request.

4.8 The EMA will check inspection reports received for adherence to this guideline and for their scientific content and overall quality. Reports, that in the opinion of the Agency are found to be deficient, incomplete or below the required scientific standard, will be returned to the authorities responsible for their preparation with a written explanation of the reasons for non-acceptance and proposed deadline for revision, re-inspection or other remedial action. For pre-authorisation inspections this deadline will take account of the overall timetable adopted for completion of the assessment of the application.

5. **Pre-submission Notification by the Applicant for a Marketing Authorisation**

In their notification of intention to submit, applicants should mention the name (including contact point) and the address of the proposed manufacturers of the active substance(s) and finished product including the site(s) in the EEA responsible for batch release of the medicinal product. If necessary a flowchart should be provided to illustrate the role of all different sites involved. All sites listed in applications should be ready for inspection from the time of submission of the application and be in compliance with EU (or equivalent) Good Manufacturing Practice (GMP).

6. **Designation of an Inspection Team and Preparation for the Inspection**

The EMA validates submissions to the centralised system and determines whether or not an inspection of the manufacturing, control, batch release and importation site(s) concerned is needed to verify compliance with GMP before a marketing authorisation or a variation can be granted. A decision is made in collaboration with the (co)rapporteur whether or not to ask the relevant committee to adopt a request for an inspection. Such requests are adopted by the committee at day 90 or at the latest by day 120, and include any specific aspects of the application, that the (co)rapporteur raises in the day 70 assessment report(s), or analogous time point for variations.

In addition the EMA ensures that manufacturing sites listed in centralised marketing authorisations that are located in third countries are routinely re-inspected in accordance with the inspection frequencies laid down in the Compilation of Community Procedures in order to verify on-going GMP compliance unless an MRA or equivalent agreement is in force. Re-inspection of sites located in the EEA or in countries where an MRA or equivalent agreement is in force is left under the responsibility of the relevant National Competent Authorities.

The EMA will designate the National Competent Authorities that will form the inspection team. Normally the lead will be taken by the Supervisory Authority supported by another authority, in particular another Supervisory Authority if there is more than one. The EMA will consult the (co)rapporteurs, and EEA inspectorates as necessary and will, particularly in the case of re-inspections, attempt to distribute the workload among the Member States.

The National Competent Authorities participating in an adopted inspection request will nominate the inspectors who will carry out the inspection using the Corporate GXP application. The National Competent Authority shall not nominate inspectors that are not included in the list of EMA experts. EMA will check the status of the experts’ nomination documentation before accepting the nominations.
When the Supervisory Authority is not able to inspect in a third country, a replacement competent authority will be found in accordance with the Community Procedure for delegation of responsibilities.

For routine re-inspections the EMA will propose an annual inspection plan in consultation with the Supervisory Authorities designed to distribute the workload evenly with support from other inspectorates as necessary.

7. Contacts With the Applicant and the Manufacturer(s) to be Inspected

Once the Committee has requested an inspection, the EMA notifies the applicant/MAH that an inspection will take place, giving details of the inspection team and asks for the inspection fees to be paid.

Payments for inspections are made in accordance with the decision on a scale of fees adopted by the Management Board under Article 53 (3) of the Regulation. For inspections outside the EU, travel costs are paid directly to the inspectorates by the applicant/MAH in accordance with Article 5 (4) of Council Regulation (EEC) 297/95, as amended. The inspectors make the arrangements directly with the manufacturer and fix an inspection date and in the case of third country inspections should notify the local competent authority. In preparation of the inspection, the manufacturer(s) or the applicant/MAH may be asked to provide information about the site and operations to be inspected (this is normally provided in a “Site Master File”). The applicant may be requested to supply a copy of relevant parts of the dossier to the inspection team.

In the case of re-inspections the EMA will draw the attention to the inspection team of any specific issues that have been identified for inspection follow up for example arising from the last inspection, sampling and testing or quality defect investigations prior to the inspection.

8. Submission of the Final Report to the Rapporteur and the EMA

One month after transmission of the inspection report to the manufacturer, the inspection team shall send their report to the EMA (by uploading and signing the report in the Corporate GXP application). The lead authority for the inspection is responsible for the issue of GMP certificates or statements of non-compliance in line with Community legislation and to update the EudraGMP database accordingly.
## History of changes to the Compilation of Procedures

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
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<tbody>
<tr>
<td>December 2003</td>
<td>First published by the European Medicines Agency on behalf of the Commission updating May 2001 version to include a new procedure for handling suspected quality defects, updated rapid alert procedure, addition of verification of validation to procedure and forms for exchange of information, and quality systems framework for EU inspectorates.</td>
</tr>
<tr>
<td>February 2004</td>
<td>Updated to include a new annex on investigational medicinal products to the procedure on the conduct of inspections together with a revised document on the training and qualifications of GMP inspectors. Both documents were developed in response to Art. 15(5) of Directive 2001/20/EC.</td>
</tr>
<tr>
<td>September 2004</td>
<td>Updated to include a minor change to section 5 on the procedure for handling rapid alerts and a consolidation of the procedure and various forms for the exchange of information. It includes a new form to be used in the event of an inspection performed in a third country with a negative outcome requiring co-ordinated administrative action throughout the Community.</td>
</tr>
<tr>
<td>February 2005</td>
<td>Revision to procedure on verification of GMP in third countries.</td>
</tr>
<tr>
<td>September 2005</td>
<td>In accordance with Art. 47 of Directive 2004/27/EC and Art. 51 of Directive 2004/28/EC amending Directives 2001/83/EC and 2001/82/EC respectively, revised Community formats for a GMP inspection report and manufacturing authorisation and a Community format for a GMP certificate were introduced. Guidance to Competent Authorities was included on when inspections of active substance manufacturers may be appropriate based on the provisions of Art. 111(1) of Directive 2001/83/EC and Art. 80(1) of Directive 2001/82/EC as amended. A small change to appendix 2 of the summary report for inspections conducted at the request of the European Medicines Agency was also been introduced. The title of the procedure for handling suspected quality defects was corrected.</td>
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<tr>
<td>Date</td>
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<tr>
<td>July 2006 (rev. 5)</td>
<td>An introduction was added together with a minor change to the procedure on rapid alerts arising from quality defects as well as enhanced formats for the Manufacturing Authorisation and GMP Certificate.</td>
</tr>
<tr>
<td>September 2006 (rev. 5 reformatted)</td>
<td>The individual documents of the Compilation were reformatted and arranged in order to facilitate individual download from the website. No changes were made to the main texts of the documents.</td>
</tr>
<tr>
<td>October 2006 (rev. 6)</td>
<td>Inclusion of a procedure, applicable to centrally authorised products, for dealing with the delegation of the performance of a GMP inspection by the Supervisory Authority to another Competent Authority.</td>
</tr>
<tr>
<td>March 2007 (rev. 7)</td>
<td>A procedure for the issue and update of GMP certificates has been added. The Content of the fabricator’s/manufacturer’s batch certificate for drugs/medicinal products exported to countries under the scope of a Mutual Recognition Agreement, and the Activity/decision diagram for inspection findings for applications under the centralised system, have been removed.</td>
</tr>
<tr>
<td>April 2008 (rev 8)</td>
<td>The Quality System Framework for GMP Inspectorates was revised to introduce a quality risk management approach following the implementation of ICH Q9 guideline.</td>
</tr>
<tr>
<td>August 2008 (rev. 9)</td>
<td>Update to Training and Qualifications of GMP Inspectors document.</td>
</tr>
<tr>
<td>March 2010 (rev. 10)</td>
<td>A new procedure was added for dealing with serious GMP non-compliance, which is in addition also intended to ensure a coordinated response to CEP withdrawals or suspensions for non-GMP reasons. The procedures for handling suspected quality defects and Rapid Alerts have been updated to include active substances, falsified medicinal products and investigational medicinal products within their scopes. The GMP inspection report format has been revised in view of an agreement that additional summary reports, previously required for inspections requested by the European Medicines Agency, no longer need to be prepared.</td>
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<tr>
<td>August 2010 (rev. 11)</td>
<td>A new procedure Training and Qualifications of Inspectors performing GDP inspections was added together with an update to the introduction in view of the addition of the first document connected with GDP inspections being added. A revised document updating and extending the Procedure for Co-ordinating Foreign and Community Pre-Authorisation Inspections during the Assessment of Applications was published (Co-ordinating GMP Inspections for centrally authorised products). This allows for the removal of the Guideline on the Preparation of Reports on GMP Inspections Requested by either the CHMP or CVMP, in view of the introduction of the Community inspection report format in March 2010.</td>
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<tr>
<td>January 2011 (rev. 12)</td>
<td>A new procedure Training and Qualification of Inspectors Performing Inspections of Wholesale Distributors was added. The overall presentation of the Compilation was consolidated into a single document.</td>
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<td>July 2011 (rev. 13)</td>
<td>Deletion of ‘Exchange of Information on Manufacturers and Manufacturing or Wholesale Distribution Authorisations Between Competent Authorities in the European Economic Area’ as agreed at the GMP/ GDP Inspectors Working Group (24-26/05/2011)</td>
</tr>
<tr>
<td>May 2012 (rev. 14)</td>
<td>New templates under the ‘Forms used by regulators’ section (Wholesale Distribution Authorisation, GDP certificates, GDP non-compliance statements) and a Registration of Manufacturer, Importer or Distributor of Active Substance (used in Medicinal Products for Human Use) template have been added to facilitate entry into the Union database as required by Directive 2011/62/EU. Procedure for Dealing with Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations has been added.</td>
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<tr>
<td>July 2012 (rev. 15)</td>
<td>The ‘Community (Union) Format for Manufacturer’s Authorisation’ has been modified to facilitate harmonised interpretation. The ‘Union Format for GMP certificate’ has been similarly modified to facilitate interpretation and also to accommodate entry of inspected manufacturing operations for active substances. The ‘Statement of Non-Compliance with GMP’ and ‘Notification of Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations’ have been made stand-alone templates under the ‘Forms used by regulators’ section. A new template under the ‘Forms used by regulators’ section has been added: ‘Request Form for the Exchange of Information on Marketing Authorisation Holders or Manufacturing Authorisation Holders between the Competent Authorities in the EEA’.</td>
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