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**Medical products: quality, safety, innovation**



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## Compilation of Union Procedures on Inspections and Exchange of Information

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# Introduction

The Compilation of Union Procedures on Inspections and Exchange of Information (hereafter referred to as 'Compilation'), 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 and GDP 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 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.

The Compilation has two parts; procedures within the Part I and other documents (e.g. interpretation documents and forms used by regulators) within the Part II. Once agreed by the GMDP Inspectors' Working Group, documents are reviewed by the European Commission and then published on its behalf by the European Medicines Agency.

To facilitate harmonisation in inspections of GMP for investigational medicinal products for human use and, where required by national legislation in accordance with Directive 91/412/EEC, for investigational veterinary medicinal products, many of the procedures on GMP also apply to investigational medicinal products and, where relevant, with modifications set out in the procedures.

Guidelines on inspections of pharmacovigilance of medicinal products are part of the Good Vigilance Practice guidelines adopted by the European Medicines Agency. Guidelines on GCP inspections are part of EudraLex, Volume 10.

The Heads of Medicines Agencies have agreed to the setting up of a joint audit programme of GMP inspectorates to verify the implementation and equivalence of EEA GMP inspectorates with relevant provisions of European Directives into national laws and consequently maintain mutual confidence in the GMP inspection systems of each member state by the other Member States, Level of compliance with the Compilation of procedures provides criteria on which the audits may be based.

Member States are obliged to take account of the Compilation by virtue of Article 3(1) of Directive (EU) 2017/1572, Article 17.1 of Regulation (EU) 2017/1569, recital (69) and article 123 of regulation 2019/6.

Some procedures within the compilation details tasks and provide guidance for the supervisory authority. For human medicinal product this is defined in the article 18 of regulation 726/2004, for the veterinary medicines the EU/EEA authorities have agreed that the supervisory authority term shall be understood as following:

In the case of medicinal products manufactured within the Union, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 40(1) of Directive 2001/83/EC and Article 88 (1) (a) and (b) of Regulation 2019/6 in respect of the medicinal product concerned.

In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC and Article 88 (1) (c) of Regulation 2019/6 to the importer, unless appropriate agreements have been made between the Union and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union.”

Similarly for active substances for human and veterinary use, the national competent authorities have agreed:

Supervisory authority for active substance manufacturing sites located in the EEA is the competent authority of the country where the site is located.

For active substance manufacturing sites located in countries outside the EEA, the competent authority of the Member State which is the supervisory authority for a medicinal product has also the responsibility for supervision and inspection of the active substance manufacturers associated with the medicinal product.

# Part I – procedures

# Quality systems framework for GMP inspectorates

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<b>Title</b>	<b>Quality systems framework for GMP inspectorates</b>
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	Not applicable

# Quality systems framework for GMP inspectorates

## 1. Introduction

- 1.1 It is important 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, the European Medicines Agency (EMA) 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 The preparation of this text 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; May 2001 Revised Compilation of Community procedures on administrative collaboration and harmonisation of inspections;
1998	Proceedings of the PIC-PIC/S (Pharmaceutical Inspection Cooperation/Scheme) seminar on quality systems for pharmaceutical inspectorates.



## **2. Purpose**

- 2.1 The primary purpose of a quality system is to ensure that adequate and equivalent quality standards are maintained throughout all Member States. 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. 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 and GDP inspections, including inspections of manufacturers and/or wholesale distributors. If relevant, this could include making decisions concerning the issue or withdrawal of authorisations for their activities, the issue or withdrawal of GMP and GDP 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 EMA and Mutual Recognition Agreement (MRA) 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 Union 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, EU 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 including timeframes mentioned in existing EU or national regulations (e.g. licensing system for manufacturing or marketing authorisations) 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 Union 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 Union 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 Union 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.

# Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making

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5. Quality assurance

<b>Title</b>	<b>Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable



# Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making

## 1. Scope

The scope of this procedure relates to the managing by EU competent authorities of reports of suspected quality defects identified in medicinal products or active pharmaceutical ingredients (API) for humans and animals.

This procedure provides detailed guidance on risk assessment methodology that can be utilised by National Competent Authorities (NCAs) in order to reach regulatory risk mitigating decisions especially in the context of Member States considering the issue of a Rapid Alert notification.

## 2. Introduction

2.1 Harmonisation of procedures utilised in defect assessment and further categorisation and rapid alert transmission is essential to:

- quickly identify the level of impact of the defect on patients/end users,
- reach a common harmonised decision among Competent Authorities,
- promote mutual reliance between Member States and partner authorities.

Revision and update of procedures are also beneficial in keeping the knowledge up to date.

2.2 Holders of an authorisation, such as manufacturers and importers of medicinal products, (as per Article 40 of Directive 2001/83/EC and Article 88 of Regulation 2019/6) are obliged to report to the concerned Competent Authorities any defect in a medicinal product within the scope of their authorisation that could result in a recall or abnormal restriction in supply (as per Article 13 of Directive (EU) / 2017/1572, or Article 13 of Directive 91/412/EEC and EU Good Manufacturing Practice guides). This includes possibly faulty manufacture, product deterioration, detection of falsified medicines or any other serious quality problems with a product. In the event of a serious or potentially life-threatening situation identified for API used as starting materials, the local, national, and/or international authorities should be also informed, and their advice sought.

2.3 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 the local, national, and/or international authorities. These reports might include quality defects on APIs used as starting materials and in addition, also adverse drug reactions 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 risk assessment.

2.4 Member States are obliged to take all appropriate measures to ensure that a medicinal product 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 134 of Regulation 2019/6).

- 2.5 Each Competent Authority should have a written procedure that covers the receipt, the managing and the risk assessment of notifications of suspected defective products and batch recalls from companies or health professionals during and outside normal working hours.
- 2.6 Each competent authority should have a team of defined qualified experts capable to perform the initial professional risk-based assessment of the quality defect in accordance with the risk posed by the quality issue.
- 2.7 It is the responsibility of the company to undertake the actions recommended by the competent authority, including market actions where warranted.
- 2.8 In case of an agreed batch recall, it is normally the responsibility of the company to recall a batch and to notify concerned authorities, professionals of the distribution chain and customers in accordance with EU Good Manufacturing Practice guides.
- 2.9 It is responsibility of the Competent Authority of the Member State in which the recall occurred to notify other authorities about the recall. Responsibilities for notifying health professionals, media and the general public may vary between Member States.
- 2.10 It is responsibility of the competent authority to oversee the company's necessary investigation to identify the root cause(s) of the quality defect.
- 2.11 The present procedure should be read in conjunction with "Procedure for managing rapid alert arising from quality defect risk assessment should be used to reach a risk-based classification" and its related Appendix I "Guidance in relation to the risk-based classification and decision-making for quality defects, recalls, rapid alerts and risk reviews".

### 3. Definitions

- 3.1 **Recall action.** The action of retrieving one or more batch (es) from the distribution chain and users. A batch recall may be partial, in that the batch is only recalled from selected distributors or users. The extent of the recall of a batch is defined by quality risk associated and can go from a recall on patients level (including owners of animals) to a recall limited to community pharmacies, veterinarians or wholesalers.. Batch recalls may or may not be accompanied by withdrawal of a marketing authorisation.
- 3.2 **Quality defect report.** A report, usually a standard template in use by the receiving authority, informing about a quality defect issue impacting one or more batch (es) of a certain medicinal product or API for human or veterinary use.
- 3.3 **Rapid Alert for Quality Defects/Recall action.** Notification of urgent information on quality defects from one competent authority to other authorities. The information transmitted can be related to a batch recall action that has been instituted in the country originating the rapid alert and may concern other authorities. A rapid alert may also concern a quality defect or other serious information, regardless of whether a recall action has been initiated in the originating country.
- 3.4 **Risk based classification.** Classification of a quality defect based on the risk posed by the issue on public and animal health.

- 3.5 **Risk based decision.** A decision made taking into consideration the risk posed by a quality defect on public and animal health and aiming at mitigating or preventing the impact.
- 3.6 **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.

## 4. Management and assessment process

### 4.1 Aim

- 4.1.1 To record, assess and classify, during and outside office hours, reports of suspected defective products and to assess and oversee appropriate corrective and preventive actions (CAPAs) with appropriate urgency.

### 4.2 Receiving quality defect report

- 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 e-mail or fax 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. A file should be created for each suspected defect in order to collect information as it becomes available. All correspondence related to the specific defect should contain in the e-mail subject line key information that facilitate immediate understanding (e.g. indication on whether the product is for human (H) or veterinary (V) use or for or (H/V). (e.g. quality defect identification number/V/product name/...).

- 4.2.3 The Competent Authority assessing the defect should make sure to obtain direct personal contacts of the main parties involved, especially the person making the report, the person coordinating action for the company (usually the Qualified Person (QP)), and, case by case, the inspector familiar with the manufacturer or importer and persons responsible for vigilance within the Competent Authority.

All relevant information obtained verbally should be confirmed in writing.

- 4.2.4 The report should be referred with minimum delay to a person(s) in charge of the initial professional risk-based assessment of the quality defect. A target time should be set for reports to be referred to this person, normally during the working day. 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.

### 4.3 Assigning a risk-based classification to the defect

- 4.3.1 A formal risk-based classification of the defect should be performed in a timely manner. The guidance contained in Part I of Appendix 1 of "Procedure for managing rapid alert arising from quality defect risk assessment should be used to reach a risk-based classification".

Three levels of risk may be assigned to quality defect issues:

1. High Risk
2. Moderate Risk
3. Low Risk

- 4.3.2 Some cases can be qualified as "non-justified" as explained in Part I of Appendix 1 of the Procedure for managing rapid alert arising from quality defect risk assessment.

If the initial professional risk assessment of the report concludes that the defect may represent a high risk issue that could warrant immediate action(s) to protect patient or animal health, the necessary urgent public health safeguarding measures should be taken without waiting for the creation of the file on the defect issue referred to in step 4.2.2 to be fully in place.

- 4.3.3 A formal risk-based classification should be assigned to all reports of quality defects.
- 4.3.4 In order to promote harmonization, the quality defect should also be classified using common standardised terminology.

#### **4.4 Risk-based decision-making**

- 4.4.1 Once a risk-based decision is made on the defect reported, after the defect is classified in one of the four levels of risk above, different types of risk control actions may be agreed. Such actions should be commensurate with the level of risk and should also take into account of potential out of stock situation and clinical issues. Part II of Appendix 1 of the Procedure for managing rapid alert arising from quality defect risk assessment.

This may involve one or more of the following actions, according to the national procedures:

- Filing without follow-up (no further action required)
- Product quarantine action (e.g. at wholesale level) - this is a precautionary and interim measure useful where insufficient information is available to make immediately a final risk-based assessment and decision. Prevents further defective units being distributed, pending the availability of sufficient information to facilitate a final decision concerning market action.
- Batch or product recalls.
- Interruption / cessation of a clinical trial.
- Cessation of certification and release of any new defective batches.

- Cessation of supply of additional units of affected batches.
- Inspection of packs for the defect (e.g. at wholesalers) - to remove those that are defective.
- Reworking of packs to remove the defect.
- Caution-in-Use Notification (CIUN) / Dear Healthcare Professional Communication (DHPC).
- Communications / statements to the general public.
- Monitoring on-going stability study.
- Assessment of other batches of the same product or other products that could be affected by the same quality defect.

Note: in some cases, especially for low risk quality defects, none of the above actions may be warranted. It may be sufficient to direct the company to focus on the root causes of the defect and to ensure that effective corrective and preventative actions (CAPAs) are implemented for it and that the authorities are duly informed of the effectiveness of the implementation.

#### **4.5 Samples**

- 4.5.1 Wherever possible and when considered useful, samples of the product(s) involved in the defect report should be obtained by the Competent Authority. The samples should be analysed by an Official Medicines Control Laboratory as agreed by the Competent Authority. In certain cases samples should be provided to the company for analysis under full supervision of the Competent Authority. Results should always be made available to all interested parties.

#### **4.6 Inspection**

- 4.6.1 If necessary, the inspector usually associated with the manufacturing or importing site is made aware of the report, and comments on general GMP compliance and on the related products.
- 4.6.2 When necessary an on-site inspection is performed to assess notably batch records of the product concerned, plant records and records of other batches or products which could also be affected.
- 4.6.3 Samples of the batch concerned, related batches and related starting materials may be taken and analysed. This could also be applied to inspections coordinated by and conducted on behalf of the European Medicines Agency.

#### **4.7 Documenting and communicating the risk-based decision**

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, the decision, based on the risk assessment of the defect as per the guidance in Part 2 of Appendix 1, should be formally documented and communicated as appropriate.

NCA's are encouraged to discuss and communicate quality defects issues among themselves as well as their risk-based decisions with other NCA's through the rapid alert network, where needed.

The exact wording of any notification (such as a product recall or a DHPC) should be checked and, if possible, agreed with the company. Particular attention should be paid to the correctness of the batch number(s), expiry dates, product names in the different countries, pharmaceutical form, strength and relevant medicinal product code (e.g. marketing authorisation number). 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.

#### **4.8 Validating the Risk-based Decision**

- 4.8.1 According to the national Competent Authority procedures, approval should be obtained for the proposed action by the relevant quality defect team or other staff within the Competent Authority.

#### **4.9 Implementing the risk-based Decision**

- 4.9.1 Refer to "Procedure for managing rapid alerts arising from quality defects risk assessment" and/or the corresponding national procedure.

#### **4.10 Follow-up**

- 4.10.1 There should be consideration of what, if any, action to take concerning the Marketing or Manufacturing Authorisations and their holders. This includes the evaluation of a possible for cause inspection, where required.
- 4.10.2 The Inspectorate/ quality defect assessment unit 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.
- 4.10.3 Completion of any follow-up actions should be checked. This can include, for example, completing and organising records and archiving according to national procedures.
- 4.10.4 At national level risk review of selected quality defect investigations should be conducted. Such risk review should be performed on a voluntary basis by competent authorities, with a view to determine whether the key risks presented by the defective medicinal product were actually identified and managed effectively. Part IV of Appendix 1 provides guidance in this regard.

## **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, in the risk-based decision-making process or in managing a Rapid Alert, should be trained in the relevant procedures and have access to a copy of the Standard Operating Procedures (SOPs) and report forms wherever they may be required to act (including at home if they are on call outside-office hour).

# Management of rapid alerts arising from quality defects risk assessment

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Notes	Pharmacovigilance or medical device alerts are not included within the scope of this procedure



# Procedure for managing rapid alerts arising from quality defects risk assessment

## 1. Scope

This procedure covers the transmission across a "Rapid Alert Network" of a rapid alert notification when urgent action is required to protect public or animal health and covers both human and veterinary medicinal products

The rapid alert may be issued to:

Figure: 1. recall of one or more batches of a medicinal product suspected of having a quality defect

Figure: 2. recall of one or more batches of a medicinal product suspected to be falsified

Figure: 3. embargo or quarantine on the distribution of products following suspension or withdrawal of a manufacturing / wholesale authorisation.

Figure: 4. transmit information such as cautions-in-use, marketing authorisation withdrawals or suspension for safety reasons which may require recall of one or more batches of product from the market.

Figure: 5. notify quality defects, fraud or falsification in active pharmaceutical ingredients

Figure: 6. notify quality defects, fraud or falsification in investigational medicinal products

Figure: 7. follow-up messages to any of the above listed categories

The rapid alert is exchanged between:

Figure: 1. Competent Authorities in the European Economic Area (EEA) (the "Member States");

Figure: 2. EU acceding countries;

Figure: 3. Mutual Recognition Agreement (MRA) countries, as this procedure operates within the scope of the relevant "Two Way Alert" programmes established between the EU and MRA partners;

Figure: 4. Authorities participating in PIC/S;

Figure: 5. the European Commission;

Figure: 6. The European Medicines Agency (EMA);

Figure: 7. International organisations (Council of Europe/EDQM, WHO).

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

## 2. Introduction

- 2.1. Each holder of an authorisation referred to in Article 40 of Directive 2001/83/EC (for medicinal products for human use), Article 61(1) of Regulation (EU) No 536/2014 (for investigational medicinal products) or Article 88 of Regulation 2019/6 (for veterinary medicinal products) is required by Article 13 of Directive (EU) 2017/1572 (for human medicinal products), Article 14 of Commission Delegated Regulation (EU) 2017/1569 (for investigational medicinal products for human use) 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.
- 2.2. In addition, for centrally authorised products, Council Regulation EC/726/2004, Article 16(2) (for human products) or Regulation 2019/6, Article 58 (10) (for veterinary products), the marketing authorisation holder is obliged to inform the European Medicines Agency of any prohibition or restriction of supply imposed by the competent authority of any country in which the medicinal product is marketed and of any new information which may influence the evaluation of the benefits and risks of the medicinal product.
- 2.3. In order to protect public health and animal health, EU authorities can avail of the "Rapid Alert System" which allows exchange of urgent information including urgent measures such as the recall of one or more defective batch (es) of a medicinal product during its marketing period or of an investigational product during clinical trials.
- 2.4. Each Competent Authority should have a written procedure for the issue, receipt, and managing of notifications of defective products, risk assessment of the quality defect, 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 potentially concerned 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. Definitions

- 3.1 **Quality defect report.** A report, usually a standard template in use by the receiving authority, informing about a quality defect issue impacting one or more batch (es) of a certain medicinal product or API for human or veterinary use.
- 3.2 **Quarantine.** Storage in separate areas, clearly marked and with access restricted to authorised personnel.
- 3.3 **Rapid Alert for Quality Defects/Recall action.** Notification of urgent information on quality defects from one competent authority to other authorities. The information transmitted can be related to a batch recall action that has been instituted in the country originating the rapid alert and may concern other authorities. A rapid alert may also concern a quality defect or other serious information, regardless of whether a recall action has been initiated in the originating country.
- 3.4 **Rapid Alert Network (RAN).** Network of competent authorities who exchange urgent information on quality defects and/or recalls related to medicinal products through the Rapid Alert System.

RAN is composed by competent Authorities in the EEA, EU acceding countries, Mutual Recognition Agreement (MRA) countries, authorities participating in PIC/S, the European Commission and international organisations (Council of Europe/EDQM, WHO).

- 3.5 **Rapid Alert System (RAS)**. System in use amongst Authorities part of the Rapid Alert Network (RAN) to transmit alert on quality defects and/or recalls related to medicinal products whose urgency and seriousness cannot be delayed. The RAS includes also the "two-way alert" system established between the EU and MRA authorities.
- 3.6 **Recall action**. The action of retrieving one or more batch (es) from the distribution chain and users. A batch recall may be partial, in that the batch is only recalled from selected distributors or users. The extent of the recall of a batch is defined by quality risk associated and can go from a recall on patients' level (including owners of animals) to a recall limited to community pharmacies, veterinarians or wholesalers. Batch recalls may or may not be accompanied by withdrawal of a marketing authorisation
- 3.7 **Supervisory Authority**. Authority located in the country where the manufacturing facilities interested by the quality defect are located. These facilities could be the sites where the issue occurred or where the batch takes place.
- 3.8 **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.
- 3.9 **Suspected falsified medicine**. Any medicine with a false representation of its
- Figure: 1. identity, including its packaging and labelling, and the name, composition and strength of any of its ingredients including excipients;
- Figure: 2. source, including its manufacturer, country of manufacturing, country of origin and its marketing authorisation holder;
- Figure: 3. history, including records and documents on distribution channels used.
- 3.10 **Withdrawal of marketing authorisation**. Interruption of placing on the market of the medicinal product by the marketing authorisation.

## 4. Criteria for issuing a rapid alert

- 4.1 The aim of the "Rapid Alert System" is to transmit urgent and serious alerts without any delay.
- 4.2 Before any Rapid Alert is issued to communicate a potential recall issue, a risk-based classification should be assigned to the rapid alert and the recall action if relevant. In this regard, the following should be noted:
- Figure: 1. The classification assigned to a recall action and to a rapid alert should reflect case urgency and seriousness.
- Figure: 2. In this context, the term 'urgency' relates to the urgency in taking a recall or other action in order to adequately protect patients, animals and users of medicines from the risks posed by quality defects in those medicines. When considering the 'urgency' of a recall action or a rapid alert, the risk-based classification that has been assigned to the quality defect report (High Risk, Moderate Risk, Low Risk) is taken into account. Refer to the procedure titled "Management and Classification of Reports of Suspected Quality Defects in Medicinal Products and Risk-based Decision Making" for more details in this regard, as well as Appendix 1 to that procedure.

4.3 There are three different risk-based classifications that may be assigned to a rapid alert (with or without a recall action) and to recall actions:

Figure: 1. Class I

Figure: 2. Class II

Figure: 3. Class III

The above risk-based classification is defined in Part III of Appendix 1.

4.4 The dissemination of the Rapid Alert takes into account the assigned class and also the countries effectively concerned by the batch (es) distribution.

## 5. Issue of a rapid alert notification

### 5.1. Responsibility

5.1.1. 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 (the issuing authority).

5.1.2. 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 occurred should lead the investigation of the defect and issue the rapid alert. If the defect occurred in a third Country, the Supervisory Authority identified by the EMA should lead the investigation of the defect and issue the rapid alert.

5.1.3. In the event of immediate danger to patients, animals, consumers or environment, the Competent Authority of the Member State where the defect was first identified should lead the investigation and issue the rapid alert.

5.1.4. In both cases the alert should include a recommendation on proposed action (s) for all affected authorities.

5.1.5. In the case of centrally authorised products and when time allows, the content of the proposed action (s) should be agreed between:

Figure: 1. the Supervisory Authority,

Figure: 2. the Issuing Authority (if different from the Supervisory Authority),

Figure: 3. the European Medicines Agency and the CxMP rapporteur.

5.1.6. In some circumstances and especially when the Supervisory Authority has conducted all the required assessment, the Member State in which the defect was first identified may delegate to the Supervisory Authority the issuing of the Rapid Alert.

5.1.7. 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.

5.1.8. In the case of parallel distribution of a centrally authorised product and where no repackaging is done, the procedure described under 4.1.2 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 4.1.2 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.

5.1.9. 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.

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

5.2.1. A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2.<sup>1</sup> 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.

5.2.2. 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:

Type of rapid alert		Class	Medicine type	Product	Action	Reference number
RapidAlert	Qdefect	I II	H or V	Name + INN	Recall	Country/Class/N°/N°
	Falsified				No Recall	
	Fraud				Follow- up	

Figure: 1. Example: RapidAlert; Qdefect; I, H; Product X; Follow-up, CH/I/07/01.

5.2.3. 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/year/sequential number/correspondence number. (For example, ES/II/2019/05/02 would indicate a class II rapid alert initiated by Spain, being the 5th rapid alert initiated by Spain in 2019 and that it is the second correspondence regarding this rapid alert.) The sequential number should reset every year.

5.2.4. Transmission of a Class I and, whenever feasible of a Class II, rapid alert must be concurrent with the national action and in all cases should be within 24 hours of the national notification.

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

<sup>1</sup> The template can be downloaded at the following link: <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice#compilation-of-union-procedures-section>

- 5.2.5. When an authority issues an additional rapid alert for a batch, the field 21 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.#".

### **5.3. Rapid alert contact list**

- 5.3.1. 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 ([gdefect@ema.europa.eu](mailto:gdefect@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.

## **6. Fraud and falsified products**

- 6.1. It is acknowledged that the meaning of words such as "falsified" and "fraud" may vary from one country to another. It is also acknowledged that, in the European Union, the meaning of "falsified medicinal product" corresponds to the definition provided by Article 1 (c) of directive 2011/62/EU.
- 6.2. 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 suspicious offer and products containing qualitative and/or quantitative different active substances than those described in the marketing authorisation.
- 6.3. The Competent Authority of the Member State or MRA partner in which the fraud or falsification was first detected should issue the Rapid Alert. 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 Rapid Alert contact list.

## **7. Follow-up action**

- 7.1. 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.
- 7.2. The relevant Supervisory Authority should investigate the circumstances that led to the manufacturing and distribution of the defective product and ensure that any necessary corrective action is taken by the manufacturer, parallel trader, wholesaler, and marketing authorisation holder as appropriate.
- 7.3. The European Medicines Agency should co-ordinate follow-up action for recalls of centrally authorised products.
- 7.4. 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 31 to separate it

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<sup>1</sup> The template can be downloaded at the following link: <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice#compilation-of-union-procedures-section>

from Rapid Alerts. It should have a reference number linking it to the original Rapid alert following the same format as described above.

## **8. Further use of rapid alert contact list**

8.1. Although the contact list for rapid alert notifications shall be only used for the transmission of notification related to product quality defects 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.

## **9. Appendices**

- 9.1. Appendix 1: Guidance in relation to the risk-based classification and decision making for quality defects, recalls, rapid alerts and risk reviews
- 9.2. Appendix 2: Format for rapid alert notification of a quality defect
- 9.3. Appendix 3: Format for follow-up and non-urgent information for quality defects

## Appendix 1: Guidance in relation to the risk-based classification and decision-making for quality defects, recalls, rapid alerts and risk reviews

This guidance addresses the following four activities:

- Part I: Risk-based classification of quality defects
- Part II: Risk-based decision-making for quality defect cases to ensure that patients and animals are adequately protected from the risks presented by defective medicines
- Part III: Risk-based classification of recalls and rapid alerts
- Part IV: Risk Review of quality defect investigations

This guidance is intended for national competent authorities (NCAs) to assist them in their investigation of quality defect reports, and in their coordination and management of product recall and other risk reducing actions, as well as rapid alerts.

It is designed to reflect the principles and concepts of Quality Risk Management (QRM) as outlined in ICH Q9. In this regard, each of the four elements of QRM (*Risk Assessment, Risk Control, Risk Review and Risk Communication*) are addressed. For example:

- In Part I, the risk-based classification of quality defects can be considered an output of Risk Assessment activities.
- In Part II, the risk-based decision-making for quality defects results in actions that control risks for patients and animals, such as product recalls and the cessation of batch certification and release until the defect issue has been resolved. Such actions can be considered to be Risk Control activities.
- The outputs of Parts II and III, such as recall letters issued to healthcare professionals, and rapid alerts issued to other competent authorities, are types of Risk Communication; they provide timely information about potentially defective medicinal products on the market, so that risk mitigating actions can be taken to protect patients and animals.
- Part IV addresses the review of quality defect investigations and data to determine whether the key risks were actually identified and managed effectively; this is an example of Risk Review activities.

Each NCA is encouraged to use this guidance when working through its quality defect cases, in order to ensure a harmonised approach to the management of quality defects across the EEA.



## Part I: Guidance in relation to the classification of quality defects

It is recommended that each quality defect case should be classified in accordance with the risks it may present to patients / animals. (This constitutes a risk assessment of the quality defect issue.) A classification should normally only be assigned after certain key information is gathered and after certain key questions have been considered. These are detailed below.

Following the receipt of a quality defect report, the NCA should work to understand and document the extent and the nature of the defect issue – an exact description of the defect should be obtained, and specific details about the medicinal product (or active substance, if the defect issue relates to an API) should be obtained. This includes the labelled product name, the pharmaceutical form, the product strength, the pack size, the batch number(s) and expiry date(s), the manufacturer(s), the authorisation status of the product, and whether it is a parallel imported / parallel distributed product.

Once information such as the above is known, the following key questions should be considered, to arrive at a risk-based classification of the defect:

### 1. In relation to the known extent of the defect:

*Note: The questions below can be considered to relate to the likelihood of occurrence of the defect in the concerned product, and the following questions should be considered:*

*Considerations on the number of units/batches impacted:*

- How widespread is the defect – is only one pack in one batch known to be affected, is the full batch likely to be affected, are multiple batches likely to be affected, are other strengths of the same product likely to be affected, etc.?
- Is the extent of the defect likely to increase throughout the remaining shelf-life of the batch? This may occur, for example, with stability-related quality defects.

*Consideration on the distribution:*

- How long has the defective batch and / or product been on the market?
- Have other quality defect reports been received at the NCA about the issue?
- Has the manufacturer / MAH received complaints from the marketplace about the defect?
- Has the manufacturer / MAH received any adverse reaction reports which could be related to the defect?
- To what level within the distribution chain has the defective batch reached, and how many units have been distributed?
- Are parallel imported / parallel distributed products and / or other products likely to be affected?
- Has the defective batch been distributed to any other market?

### 2. In relation to the nature of the concerned product:

*Note: The questions below can be considered to relate to the intrinsic risk that is presented by the concerned product, and the following questions are designed to help understand that risk:*

*Considerations on medicines intended for human use:*

Typology of product:

- Is it a non-sterile product or is it a product expected to be sterile? If sterile, is it terminally sterilised or aseptically prepared?
- Is it a cold-chain product?
- Is this a critical lifesaving / emergency treatment product, where there would be an acute danger to patient or animal health in the event of a quality defect (e.g. adrenaline injections, where a failure to deliver the dose could lead to patient harm)?
- What is the therapeutic class of the product? Is the product typically used for the long-term treatment of chronic diseases?
- Is the product an immediate release or a prolonged release formulation? (This can be important for stability and compositional-related quality defects.)
- Does the product have a narrow therapeutic index?

Typology of administration:

- Is the product self-administered or is it administered only by HCPs?
- Is the product complex to administer?
- What is the route of administration of the product - parenteral, oral, intrathecal, etc? Might this influence the risks presented by the defect?
- Does the defect pose a risk to those who administer the product – e.g. in case of accidental injection, inhalation, skin contact (e.g. cytotoxics), etc.?

*Considerations on medicines intended for veterinary use:*

- What is its criticality? For example, is it a non-critical product such as 'zootechnic' product (e.g. one used to manage female reproduction), or is it one that is considered clinically critical?
- Is the product given to food producing animals?
- Is the product used for mass herd / flock treatment, or to treat zoonotic diseases, or in disease eradication campaigns?

*Other general considerations:*

- Are there any indications that the quality defect issue might be the result of falsification activities?

**3. In relation to the patient groups potentially exposed to the defective units:**

*Note: The questions below can be considered to relate to the severity of the consequences of the quality defect on patients or animals.*

- Are they high risk / vulnerable patient groups, such as neonates, immuno-compromised patients, children, etc.?

- Are the patients who use this product routinely monitored by a HCP?
- What is the general level of familiarity of patients in using the product?
- If it is a veterinary product, have the exposed animals a substantial value (e.g. racing horses, breeders, etc.)?

#### **4. In relation to the quality defect itself:**

*Note: The questions below can be considered to relate to the severity of the consequences of the quality defect on patients or animals, or to the detectability of the issue.*

*Considerations on the harm posed by the defect:*

- How might the defect be expected to cause harm / injury - might it lead to under-dose, overdose, no dose, toxic effects, contaminants being ingested, administration errors, etc.?
- What is the likelihood that harm / injury may occur from exposure to the defective medicine?
- Is there a risk of harm to the person administering the defective product?
- Is there evidence that harm has actually occurred? Have any adverse reactions been reported that may be attributable to the defect issue?
- Is the defect readily detectable? (Caution – detectability should not be relied upon too much, because it is known that patients and HCPs still sometimes use defective products even when the defect is obvious and highly detectable.)
- What are the potential consequences of the defect? Illness, mistreatment / lack of treatment, lack of efficacy, infection, injury, death, no consequences, etc.?
- For veterinary medicines in food-producing animals, does the defect relate to the labelled withdrawal periods?

Other considerations:

- What is the risk posed to patients / animals if they do not take / receive the product?
- Does the defect relate to a non-compliance issue – such as the failure to implement a marketing authorisation variation, or a failure to comply with GMP? If yes, how serious is this failure?

*Note: It is not intended that all of the above questions have to be addressed in every quality defect investigation – they are presented here as useful things to consider, but their relevance depends on the nature of the defect in question.*

When the relevant questions above have been considered, the High / Moderate / Low Risk classification system outlined below should be used and a classification assigned to the defect issue.

## Classification system for quality defects

**High risk quality defects** are defects which are potentially life-threatening or could cause serious risk to health.

Examples of such quality defects include:

- 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 or microbial contamination of any medicinal product which is administered to, or taken by, immuno-compromised patients or animals.
- Chemical contamination with serious medical consequences.
- Mix up of products ('rogues') within a pack. For example, two different blister strips within one outer carton, or, two different tablets within the one blister strip.
- Wrong active substance in a multi-component product with serious medical consequences.
- Serious adverse reactions which are batch or product related (most likely to be first notified to the Pharmacovigilance Department in an urgent safety report).
- The quality defect renders a life-saving product impossible to use, e.g. adrenaline, insulin, etc.
- The defect presents a high risk to those who may administer the product to patients or animals
- The defect presents a high environmental risk.
- Presence of particles in injectable medicinal products.

**Moderate risk quality defects** are defects which could cause illness or mistreatment with potentially non-serious medical consequences but are not classified as critical.

Examples of such quality defects include:

- Mislabeling issues - wrong or missing text or figures.
- Missing or incorrect information relating to labels, leaflets or pack inserts.
- Microbial contamination of products that are intended to be non-sterile, with potentially non-serious medical consequences.
- Chemical / physical contamination (significant impurities, cross-contamination, particulates).
- Mix up of products ('rogues'). For example, a case of product A contains one or more packs of product B) but A & B are very similar products (e.g. generic versions of a product) and the mix-up does not pose a clinical risk.
- Non-compliance with specification (e.g. assay, stability, fill / weight), with risk of lack of efficacy or toxicity. Note: certain lack of efficacy and toxicity issues might be considered to be high risk.
- Unsecured closure with non-serious medical consequences.

- Wrong withdrawal period for a veterinary medicine with moderate risk to animal-derived food products (e.g., milk, meat) – this would be where the withdrawal period is labelled as being shorter than that which is authorised.
- Significant OOT stability test results where batches on the market are likely to go out-of-specification before they expire.

**Low risk quality defects** are defects which are not likely to pose a significant hazard to health.

Examples of such quality defects include:

- Unclear labelling, minor labelling errors.
- Over-labelling of expiry dates or other information that is executed incorrectly.
- Faulty closures, where no increased risk to the quality of the product is presented.
- Wrong withdrawal period for a veterinary medicine with little or no potential risk to animal-derived food products (e.g. milk, meat) – this would be where the withdrawal period is labelled as being longer than that which is authorised.
- Under-filled or over-filled containers/packs which do not pose a clinical risk.
- Marginal OOS results at the end of the product shelf-life.

Note that the classification that is assigned to a quality defect issue is often largely influenced by the nature of the product concerned, and the classification may not always align with the above examples.

**Non-justified quality defects** are defect reports which could not be substantiated, and which were not true quality defects when they were investigated.

Examples of non-justified quality defects include:

- Reports in relation to the over-labelling on parallel import packs, when the over-labelling is actually in compliance with the parallel import authorisation.
- Reports of crystallisation in a product where crystallisation is a known phenomenon with that product and where the product information (e.g. package leaflet, Summary of Product Characteristics (SmPC), etc.) provides information on how to deal with that.
- Reports that relate to the misuse of the product.

*Note: The High, Moderate and Low risk classifications are assigned to confirmed quality defect reports. The Non-justified classification is assigned to a quality defect report which, when investigated, is found not to be a confirmed quality defect. However, if there is any doubt as to whether the report is a valid report, a cautious approach should be taken, and it should be assumed that the report is valid. In such cases, the defect should be classified as a high, moderate or low risk quality defect.*

The next part of this guidance relates to making risk-based decisions to ensure that patients and animals are adequately protected from the risks presented by defective medicines.

## **Part II: Guidance in relation to the risk-based decision making for a defect case to ensure that patients and animals are adequately protected**

This part concerns decision-making that is designed to control and manage the risks that are presented by defective medicinal products. Different types of risk control actions may be taken in this regard (e.g. a product recall), but before they are considered, the following key questions should first be considered:

Considerations on the typology of defect and medicinal product:

- What classification has been assigned to the defect? (This is a general reflection of its seriousness.)
- Is the defect likely to exacerbate over time, potentially altering the risk posed by the defect throughout the remaining shelf-life of the batch? (This can be relevant to stability-related quality defects).
- If there is a clinical trial involved, is the risk presented by the issue sufficient to warrant a cessation of the trial?
- What is the method of sale and supply of the product?
- What is the remaining shelf-life of the defective batch?

Considerations on regulatory actions:

- If a recall action is being considered, how far into the distribution chain should it extend – to patient / user level, to pharmacies / hospitals only, to veterinarians, to wholesalers only, etc.? In other words, what type of recall action would be commensurate with the risks presented by the defect?
- What were the dates of first distribution of the defective batch (es) – is it likely that there are few, if any, packs of the defective product still remaining in the marketplace? What is the expected timeframe for any remaining units to become exhausted?
- Should an OMCL be asked to test or examine the product before a decision on market action should be made?
- If no market action is considered necessary, should the manufacturer be formally requested to cease the release of new batches of the product until it is assured that the defect issue has been addressed?
- Would it be appropriate to ask the manufacturer or wholesaler to inspect the packs under their control to identify any defective units and to allow them to market the remaining, defect-free packs?

Considerations on possible market disruptions:

- Is the issue so serious that a recall action justified even if it leaves the marketplace and patients with none of the medicine?

- If it is essential to ensure continuity of supply of the medicine, is there adequate replacement stock of defect-free product available to ensure this, in the event that the defective batch(es) is(are) recalled?
- Would the risks to patients / animals be higher if the product was not available versus leaving the defective packs in the marketplace?
- Is a therapeutically alternative product available and, if so, can patients / animals be switched to the alternative? (Note: Clinical expertise should be sought when considering this question.)

Considerations on communication to healthcare providers and/or patients:

- How readily detectable is the defect issue? (Caution – detectability should not be relied upon too much here, because it is known that patients and HCPs still sometimes use defective products even when the defect is obvious and highly evident.)
- Could the risks to patients or animals be adequately managed by a Caution-in-Use / Dear HCP Communication?

Having considered the above questions, a decision should be made as to what risk control action(s), if any, may best serve to manage the risks presented by the defective product, taking into account the need to be commensurate with the level of risk. (Note: NCAs are encouraged to discuss and communicate their risk-based decisions with other NCAs, where feasible.)

- Filing without follow-up (no further action required)
- Product quarantine action (e.g. at wholesale level) - this is a precautionary and interim measure useful where insufficient information is available to make immediately a final risk-based assessment and decision. Prevents further defective units being distributed, pending the availability of sufficient information to facilitate a final decision concerning market action.
- Batch or product recalls.
- Interruption / cessation of a clinical trial.
- Cessation of certification and release of any new defective batches.
- Cessation of supply of additional units of affected batches.
- Inspection of packs for the defect (e.g. at wholesalers) - to remove those that are defective.
- Reworking of packs to remove the defect.
- Caution-in-Use Notification (CIUN) / Dear Healthcare Professional Communication (DHPC).
- Communications / statements to the general public.
- Monitoring on-going stability study.
- Assessment of other batches of the same product or other products that could be affected by the same quality defect.

*Note: In some cases, especially for low risk quality defects, none of the above actions may be warranted, and it may be sufficient to direct the company to focus on the root causes of the defect and to ensure that effective CAPAs are implemented for it.*



## Part III: Risk-based classification of recalls and rapid alerts

*Note: this guidance is intended to support the procedures in the Compilation of Union Procedures in relation to Rapid Alerts.*

- It is recommended that each recall action and each rapid alert should be classified according to its urgency and seriousness.
- In this context, the term 'urgency' relates to the urgency in taking a recall or other action in order to adequately protect patients, animals and users of medicines from the risks posed by quality defects in those medicines.
- When considering the 'seriousness' of a recall action or a rapid alert, the risk-based classification that has been assigned to the quality defect issue – e.g. High Risk, Moderate Risk, Low Risk – should be taken into account.
- The following classification system should be used for recall actions and rapid alerts:
  - **A Class I rapid alert/recall action** relates to a potentially life-threatening issue. If a recall is required, it generally relates to high risk quality defect issues. When needed, they should extend to patient / user level, and cover all actors in the distribution network for the concerned product, e.g. all relevant wholesalers, retailers (pharmacies, veterinarians), clinics, etc., but the extent of the recall action depends on the extent of distribution of the defective product. A Class I 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.
  - **A Class II rapid alert/recall action** generally relates to an issue that could cause illness or mistreatment, but which does not warrant a Class I alert/recall. In case of recall, this generally relates to moderate risk quality defect issues. They should normally extend to pharmacy / retail level and cover all previous actors in the distribution network for the concerned product, e.g. all relevant wholesalers. Note that the extent of the recall action depends on the extent of distribution of the defective product. A Class II rapid alert notification should be sent to the rapid alert contacts of the countries to where the defective product was distributed. But, in cases where it is difficult to know where a batch has been distributed, the notification should be sent to all contacts in the rapid alert notification list. The potential for parallel distribution of the affected batch (es) should be taken into account when considering whether to send the rapid alert to all contacts in the rapid alert network.
  - **A Class III rapid alert/recall action** concerns an issue that may not pose a significant hazard to health. In this case a recall may be initiated for other reasons. Such recalls generally relate to low risk quality defect issues. They should normally extend to wholesaler level only. These are not notified through the Rapid Alert System.

## **Part IV: Risk review of quality defect investigations and related data**

This Part addresses the review of quality defect investigations and their assessment to determine whether the key risks presented by the defective medicinal product were actually identified and managed effectively. Such risk reviews would be performed on a voluntary basis by Competent Authorities.

Each NCA should ensure that the following actions in this regard are performed:

- A sample of investigations concerning high risk quality defects, including Class I recalls and rapid alert cases, should be subjected to a formal risk review exercise.
- The risk review exercise should consider the following:
  - Whether the decisions made in the managing of those quality defect cases were adequate, taking into account all available information at the time;
  - Whether the risk-reducing actions that were taken at the time (if any) were commensurate with the level of risk that the quality defect presented to patients, users or animals;
  - Whether any risk acceptance decisions that were made at the time can still be considered to be justified;
  - Whether any new knowledge, experience or other information was received since the initial risk assessment which might alter the risk level that was determined for the quality defect issue at the time;
  - Whether any events occurred since the initial risk assessment that might impact the original quality risk management decision.
- The timing of such risk review exercises should be determined on a case-by-case basis, taking into account the level of risk that was estimated for the quality defect issue. It is suggested that high risk quality defect investigations should generally be reviewed within a period of 3-6 months after their receipt.

## Appendix 2: Format for rapid alert notification of a quality defect

Appendix 2			
<b>IMPORTANT: DELIVER IMMEDIATELY- Rapid alert notification of a Quality Defect/Recall</b>			
<div style="border: 1px solid black; height: 40px; width: 100%;"></div> <p style="font-size: small; margin-top: 5px;">Add letter head of sender</p>	<p><b>1. Reference Number</b> <input style="width: 100%;" type="text"/></p> <p><b>2. Recall Number Assigned (if available)</b> <input style="width: 100%;" type="text"/></p>		
<p><input type="checkbox"/> + <input type="checkbox"/> - <input style="width: 100%;" type="text"/></p>		<input type="button" value="Attach file"/>	
<p><b>3. To:</b> (see list attached, if more than one) <input style="width: 100%;" type="text"/></p>		<p><b>4. Files attached?</b> <input style="width: 100%;" type="text"/></p>	
<p><b>5. For use in</b> <input style="width: 100%;" type="text"/></p>	<p><b>6. Product recall/class of defect</b> <input style="width: 100%;" type="text"/></p>	<p><b>7. Reason</b> <input style="width: 100%;" type="text"/></p>	
<p><input type="checkbox"/> + Product <input type="checkbox"/> - Product</p>			
1	<b>8. Product</b>	<b>9. Strength</b>	<b>10. INN or Generic name</b>
	<b>11. Pack size and Presentation</b>	<b>12. Brand/Trade Name</b>	<b>13. Dosage Form</b>
	<b>14. Marketing Authorisation Number</b>	<input style="width: 100%;" type="text"/>	
<p><input type="checkbox"/> + Batch <input type="checkbox"/> - Batch</p>			
1.1	<b>15. Batch Number (and bulk, if different)</b>	<b>16. Date manufactured</b>	<b>17. Expiry Date</b>
	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>
<b>18. Marketing Authorisation Holder</b>		<b>19. Manufacturer</b>	
Name	<input style="width: 100%;" type="text"/>	Name	<input style="width: 100%;" type="text"/>
Address	<input style="width: 100%;" type="text"/>	Address	<input style="width: 100%;" type="text"/>
E-mail	<input style="width: 100%;" type="text"/>	E-mail	<input style="width: 100%;" type="text"/>
Phone	<input style="width: 100%;" type="text"/>	Phone	<input style="width: 100%;" type="text"/>
<b>20. Recalling Firm (if different)</b>		<b>21. Site where the defect occurred (where the defect is attributed to a manufacturing site and if different from 19)</b>	
Name	<input style="width: 100%;" type="text"/>	Name	<input style="width: 100%;" type="text"/>
Address	<input style="width: 100%;" type="text"/>	Address	<input style="width: 100%;" type="text"/>
E-mail	<input style="width: 100%;" type="text"/>	E-mail	<input style="width: 100%;" type="text"/>
Phone	<input style="width: 100%;" type="text"/>	Phone	<input style="width: 100%;" type="text"/>
<b>22. Details of the Defect/Reason for the Recall</b>			
<input style="width: 100%; height: 20px;" type="text"/>			
<b>23. Information on Distribution including exports (type of customer, including parallel distribution/importation)</b>			
<input style="width: 100%; height: 20px;" type="text"/>			
<b>24. Action Taken by the Issuing Authority</b>		<b>25. Proposed Action</b>	
<input style="width: 100%; height: 20px;" type="text"/>		<input style="width: 100%; height: 20px;" type="text"/>	
<b>26. Issuing Authority</b>			
From (Issuing Authority)	<input style="width: 100%;" type="text"/>	Phone	<input style="width: 100%;" type="text"/>
Contact person	<input style="width: 100%;" type="text"/>	E-mail	<input style="width: 100%;" type="text"/>
Signature	<input style="width: 100%;" type="text"/>		<b>27. Date/Time</b> <input style="width: 100%;" type="text"/>

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## Appendix 3: Format for follow-up and non-urgent information for quality defects

Appendix 3		
Follow-up and Non-urgent Information for Quality Defects		
Add letter head of sender	1. National Reference Number (when applicable)	
	2. Recall Number Assigned	
<input type="button" value="+"/> <input type="button" value="-"/>		<input type="button" value="Attach files"/>
3. To: (see list attached, if more than one)	<input type="text"/>	4. Files attached? <input type="text"/>
<input type="button" value="+ Product"/> <input type="button" value="- Product"/>		
1	5. Product	6. Strength
	<input type="text"/>	<input type="text"/>
	8. Brand/Trade Name	7. INN or Generic name
	<input type="text"/>	<input type="text"/>
	9. Dosage form	10. Marketing Authorisation Number
	<input type="text"/>	<input type="text"/>
<input type="button" value="+ Batch"/> <input type="button" value="- Batch"/>		
	11. Batch number (and bulk, if different)	
1.1	<input type="text"/>	
12. Marketing Authorisation Holder		13. Manufacturer
Name	<input type="text"/>	Name
Address	<input type="text"/>	Address
E-mail	<input type="text"/>	E-mail
Phone	<input type="text"/>	Phone
14. Subject title		
<input type="text"/>		
15. Issuing Authority Contact Person		
From (Issuing Authority)	<input type="text"/>	
Contact Person	<input type="text"/>	E-mail <input type="text"/>
Phone	<input type="text"/>	16. Date/Time <input type="text"/>
	Signature	<input type="text"/>

# Conduct of inspections of pharmaceutical manufacturers or importers

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1. Introduction
2. General considerations on inspections
3. Inspection planning and preparation
4. Inspection steps
5. Final meeting
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9. Glossary of terms

<b>Title</b>	<b>Conduct of inspections of pharmaceutical manufacturers or importers</b>
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Supersedes	Version adopted in January 2010
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Original guideline December 1996. Annex on Investigational Medicinal Products adopted in October 2002 and entered into force in May 2004

# Conduct of inspections of pharmaceutical manufacturers or importers

## 1. Introduction

In line with Articles 42 and 111 of Directive 2001/83/EC and Articles 90 and 123 of Regulation 2019/6, and Article 3 of Directive 91/412:EEC inspections are performed at manufacturers and importers of medicinal products and in line with Article 63(4) of Regulation (EU) No 536/2014 and, for investigational veterinary medicinal product, where national legislation requires, inspections are performed at manufacturers and importers of investigational medicinal products.

In addition, Article 111 of Directive 2001/83/EC and Article 123 of Regulation 2019/6 include provisions for inspections of manufacturers and importers of active substances used as starting materials<sup>1</sup>.

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 this 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 Union 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 and clinical trial 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.

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<sup>1</sup> Following Article 46a of Directive 2001/83/EC and Article 95 of Regulation 2019/6 , 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 Union 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 (EudraGMDP, 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);
- identify some of the documentation which may be required during the inspection.



During the opening meeting, which normally should take no more than 30 minutes, the company should:

- describe the Quality Management System, when requested;
- explain significant changes in facilities, equipment, products and personnel since the last inspection;
- explain how deficiencies have been resolved if this information has not already been forwarded to the competent authority;
- designate the people to accompany the inspector during the inspection;
- allocate a room for the inspector when requested.

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 as amended and Article 93 (2) of Regulation 2019/6 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 Union 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 Union 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 Union, Volume 4 are applicable to this document. In addition, the following apply:

**Inspection:** On-site assessment of the compliance with the Union GMP principles performed by officials of Union 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 88 of Regulation 2019/6 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 30 of Regulation 2019/6 or Article 61(1) of Regulation (EU) No 536/2014 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 (EU) 2017/1572, Delegated Regulation (EU) 2017/1569 and/or 91/412/EEC and whether the manufacturer is acceptable for the products in question. The Union report format applies.

# Appendix 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 Union 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:

- Verification that the proposed manufacturer holds the appropriate manufacturing authorisations for the product concerned (Article 40 of Directive 2001/83/EC and Article 88 of Regulation 2019/6).
- Verification that the appropriate authorisation is held where third country importation is proposed (Article 40 of Directive 2001/83/EC and Article 88 of Regulation 2019/6).
- Verification that any Quality Control laboratory has been inspected and approved (Article 20(b) of Directive 2001/83/EC or Article 30 of Regulation 2019/6), 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 (Article 5 of Directive (EU) 2017/1572 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 Union, Volume 4, recommends that trend evaluation of analytical test results be carried out. If this has been done the evaluation should be reviewed.

## Appendix 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 61 (1) of Regulation (EU) No 536/2014 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 63 (4) of Regulation (EU) No 536/2014. In both cases the inspection is carried out on behalf of the European Union and the outcome is recognised by all Member States.

Article 63(1) of Regulation (EU) No 536/2014 provides that investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial. In some cases, there will be an overlap between Good Manufacturing Practice 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 5.1 of Regulation (EU) No 536/2014 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 Union 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 5.1 of Regulation (EU) No 536/2014 .

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:

Figure: 1. 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.

Figure: 2. 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:

Figure: 1. Product Specification Files;

Figure: 2. 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:

Figure: 1. Standard operating procedures ('SOP's);

Figure: 2. 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.

## Appendix 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 123 of Regulation 2019/6 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.

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 Union 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 pharmacopoeial 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 46a of Directive 2001/83/EC as including both:

- total and partial manufacture or import of an active substance used as a starting material;

Figure: 1. 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.

The EU supervisory authorities have agreed that according to Articles 4 (3) and 95 of Regulation 2019/6, the above definition is applicable to the manufacture of active substances used as starting materials in veterinary medicinal products.

Inspections will therefore be performed of sites producing active substances and also those where active substances are being imported, repackaged or relabelled.

It should be noted that Part II of the EU Guidelines to Good Manufacturing Practice is only applicable to the manufacturing steps prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances should be performed in accordance with the principles and guidelines of GMP as laid down in Directives 91/412/ECC, (EU) 2017/1572 and Delegated Regulation (EU) 2017/1569 respectively, and interpreted in Part I of 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 Part II 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 Union 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:

Figure: 1. 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;

Figure: 2. 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);

Figure: 3. 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:

Figure: 4. job descriptions and training of staff;

Figure: 5. standard operating procedures (SOPs);

Figure: 6. qualification reports;

Figure: 7. validation reports;

Figure: 8. manufacturing formulae, records and instructions;

Figure: 9. reprocessing, reworking and solvent recovery SOPs;

Figure: 10. specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products;

Figure: 11. product quality review;

Figure: 12. batch release;

Figure: 13. complaints;

Figure: 14. recalls.

For sites that are importing, repackaging and labelling 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 123 of Regulation 2019/6 a competent authorities should perform an inspection 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.

# Outline of a procedure for co-ordinating the verification of the GMP status of manufacturers in third countries

## Table of contents:

1. Verification of the GMP compliance status of third country manufacturers of medicinal and investigational medicinal products
2. Exchange of information on third country manufacturers
3. Organisation and records of inspections and composition of inspection teams
4. Communication between the "supervisory authority" and industry
5. The "supervisory authorities"
6. Re-inspection frequency
7. Disagreement between Member States on acceptability of inspection reports
8. Annex

<b>Title</b>	<b>Outline of a procedure for co-ordinating the verification of the GMP status of manufacturers in third countries</b>
Date of adoption	May 2023
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Supersedes	Version adopted on 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Minor updates were done in the section Communication Between the "Supervisory Authority" and Industry
Notes	Not applicable

# 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 evaluation is undertaken product-specifically and includes information obtained from MRA countries and 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 Union 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 Union and the Competent Authorities of the MRA country in which the manufacturer is located.

or

1.1.5. Either an inspection report with a clear GMP statement or a statement of GMP compliance obtained under an operational Mutual Recognition Agreement between the European Union and the Competent Authorities of an MRA country, if the scope of the operational Mutual Recognition Agreement includes those third country inspections and is not limited by territorial rules to the jurisdiction of the MRA partner. If products and production lines in question were not covered by the MRA partners inspection an EEA inspection may be considered by the EU/EEA Supervisory Authority.

If a GMP certificate has been issued by an MRA partner, the regulatory authority performing the verification of the GMP compliance status should obtain this document as a minimum. The GMP certificate should not be older than three years and may be obtained from a central repository (e.g. EudraGMDP database), the issuing MRA partner or the manufacturing site and be verified with the issuing MRA partner. If this GMP certificate obtained has a satisfactory level of detail, it can be accepted.

### 1.2 Triggers and risk factors for an onsite inspection

The following are examples of possible triggers or risk factors for an onsite inspection:

- There is no inspection history for the site.
- The site was not inspected by an EEA inspectorate or the MRA partner.

- The GMP certificate / available inspection report does not cover products or processes / activities that are of interest to the regulatory authority performing the assessment.
- There is evidence that another regulatory authority has not approved the manufacturing facility, or even aspects of it (e.g. sterile vs non-sterile areas).

This is not an exhaustive list and decisions on whether or not to perform an onsite inspection should be made on a case-by-case basis taking into consideration the available information and triggers and risk factors defined within national/regional procedures. (See also the Union procedures: *A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers* and *Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials*)

1.3 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.

1.4 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:

1.4.1 Under the provisions of some 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 those 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 3<sup>rd</sup> country manufacturer operates to an equivalent level of GMP.

1.4.2 Under the provisions of some of the existing MRAs, information from MRA partners can be or is accepted in connection with inspections performed in third countries.

During national or international public health emergencies or other crises, on-site GMP/GDP inspections may not be possible for a number of reasons such as travel restrictions, risk to health, or other restrictions/guidance issued by local or national authorities. During these situations, the obligation of manufacturers, importers and distributors to comply with GMP/GDP is not waived and the ongoing verification of compliance by Supervisory Authorities is important to ensure the protection of public health.

In these circumstances, taking into account national and European legislation, distant assessments can represent a suitable means of determining compliance with the principles and guidelines of GMP/GDP. The guidance<sup>1</sup> (Guidance related to GMP/GDP and PMF distant assessments ) should be followed by the supervisory authority.

## 1.5 Investigational Medicinal Products

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<sup>1</sup> Guidance related to GMP/GDP and PMF distant assessments- [https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-related-gmp/gdp-pmf-distant-assessments\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-related-gmp/gdp-pmf-distant-assessments_en.pdf)



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 1.2 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.

## **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 EMA 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.

## **Organisation and Records of Inspections and Composition of Inspection Teams.**

- 3.1 The EMA 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 EMA 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.

## **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.

## **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. 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. Additional information on the agreed definition of "Supervisory Authorities" for products for veterinary use can be found in the *Introduction*.

## **Re-assessment frequency**

It is the responsibility of the MIA Holder to confirm that active substances used as starting materials have been manufactured in accordance with good manufacturing practice.

Unless otherwise required by the national competent authority, there is no obligation to apply the following requirements to manufacturers of active substances located in a third country.

- 6.1 In general authorities with supervisory responsibility for a third country manufacturing site should ensure that it holds a valid GMP certificate (or equivalent document(s) from MRA partners).
- 6.2 Where valid GMP certificates (or equivalent document(s)) are available,, it should not be necessary to withhold any application or variation pending the results of a recent inspection unless information is available suggesting that this status of GMP compliance may have changed.
- 6.3 GMP certificates (or equivalent document(s))based on inspections conducted more than five years ago, from whatever source, should not normally be taken into consideration.

## 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 122 of Directive 2001/83/EC. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the same arbitration procedure set out in article 122 of Directive 2001/83/EC for human medicinal products.

## 2. Annex

### SCHEME FOR DISTANT ASSESSMENT OF MANUFACTURING SITES

<b>Requirements / Rationale</b>	<b>Documentation to be requested</b>
<b>Presentation of GMP and Regulatory Enforcement system for the country</b>	Brief presentation of changes being effected since the last inspection
<b>Copy of the manufacturing authorisation granted by local authorities together with a certified translation</b>	Copy of any new/modified manufacturing authorisation granted since the last inspection
<b>SMF (site master file) documentation similar to the PIC/S guideline</b>	SMF updated with one year from the assessment date And forecasted modifications
<b>Plans attached to SMF PI&amp;D attached to SMF</b>	Coloured updated printouts may be acceptable in A3 or A2 format
<b>List of all the products (medicinal or either) manufactured on site</b>	The list may include proprietary names and INN
<b>Copy of the last inspection report with a certified translated copy if relevant GMP certificates coming from these inspections</b>	Last local authority report and last EU full report. PIC/S and WHO or FDA report(s) if aged less than 5 years
<b>Photographic presentation of manufacturing site and utilities (outdoor/indoor)</b>	Photographic presentation of any new room(s) of equipment not used at the time of inspection
<b>Qualification Master Plan (premises &amp; equipment)</b>	List of all re-qualifications exercises carried out since the last inspection
<b>Validation Master Plan (Manufacturing processes, cleaning, quality control)</b>	List of all re-validations runs carried out since the last inspection
<b>Full audit report of corporate / external audit dedicated to the product(s)</b>	The report may be aged less than 5 years and accompanied with a recent follow-up internal report

<b>Batch record(s) of the product(s) of interest</b>	Last filled in batch record including the analytical part
<b>Complaints handling</b>	Updated list of complaints of the concerned products
<b>Others *</b>	Number of rejected batches for all products Number of rejected batches for the concerned product
<b>Others</b> (concerning the concerned product / dosage form)	Out of specification procedures On-going stability studies All OOs results and investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*
<b>Others</b>	Q.P certification that site has been fully audited against EU GMP in the last 2 years and all deficiencies have been rectified
<b>Others</b>	All Q.C results for batches imported and tested in the member state.
<b>According to EU draft</b>	Product Quality Review
<b>Manufacturing Contract between manufacturing site and European applicant</b>	Original contract and revision if applicable

\*data to be provided over a period of the last 3 years

# Guideline on training and qualifications of GMP inspectors

## Table of contents:

1. Introduction
2. Scope
3. Background
4. Qualification and training
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6. Harmonisation within EU

<b>Title</b>	<b>Guideline on training and qualifications of GMP inspectors</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted June 2008
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# 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 Regulation (EU) No 536/2014) 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 Union 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, Regulation (EU) 2019/6 and Regulation (EU) No 536/2014. 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 EMA 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.

### 3.2 Personal qualities:

The inter-personal 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. 97 of Regulation 2019/6 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 Union 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:

- Union 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 Union 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 Union 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 EMA 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 Union requirements should be 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 periodically 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.

# Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials

## Table of contents:

1. Introduction
2. Purpose
3. Scope
4. Principle
5. Supervisory authority
6. Examples of inspection triggers

<b>Title</b>	<b>Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
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Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# **Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials**

## **1. Introduction**

The legal basis for the regulation of medicinal products for human and veterinary use is determined by the Union Directive 2001/83/EC and Regulation 2019/6, respectively.

Directive 2001/83/EC has been amended several times in order to permit the inspection by Competent Authorities, under certain circumstances, of premises used to manufacture, import and distribute active substances. Regulation 2019/6 has updated the regulatory framework for inspection. The competent authorities of the Member States have now the power to perform inspections at all stages of production, distribution and use of veterinary medicinal products in order to verify the compliance with the legal requirements.

The Directive 2011/62/EU on falsified medicines for human use has had a deep impact on the Directive 2001/83/EC: a lot of additional requirements regarding active substances and excipients have been introduced in order to prevent the entry into the legal supply chain of falsified medicinal products which made it necessary to revise this guidance.

Article 111(1b) of the Directive 2001/83/EC and article 123 (3) of Regulation 2019/6 stipulate for the competent authorities of the Member States to have a system of supervision in place, including by means of inspections at an appropriate frequency based on risk at the premises of the manufacturers, importers, or distributors of active substances, located on their territory, and an effective follow-up thereof. The Compilation procedure 'A Model for Risk-Based Planning for Inspections of Pharmaceutical Manufacturers' should be used as the basis for developing and implementing its own inspection programme.

## **2. Purpose**

The purpose of this guidance is to encourage uniformity of approach regarding the decision making process as to when an (additional) inspection of a company which manufactures, imports or distributes active substances and manufactures or imports excipients may be appropriate. Repackaging or relabelling of active substances and excipients are considered as manufacturing activities.

## **3. Scope<sup>1</sup>**

The scope of this guidance covers the inspection activities by Member State Competent Authorities in relation to manufacturers and importers of active substances with respect to their intended use (manufacture for human and/or veterinary medicinal products) and origin. This guidance applies to

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<sup>1</sup> Please note that wherever there is a reference to distribution and importation of active substances or manufacture, distribution and importation of excipients in the text, this is applicable to human medicinal products only. Also, where the text of this guidance refers to 'regular supervision of active substance manufacturers, importers and distributors by the competent authority in their own Member State', this is similarly applicable only to human medicinal products only.

active substances manufactured inside and outside of the European Economic Area (EEA). Regarding medicinal products for human use the scope also includes activities carried out by distributors of active substances as well as activities of manufacturers and importers of excipients.

When a Mutual Recognition Agreement (MRA) or an Agreement on Conformity Assessment and Acceptance of Industrial Products (ACAA) 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 and distribution practice for active substances used as starting materials. Based on a formalised risk assessment it has to be proved additionally by the holder of a manufacturing authorisation for human medicinal products that the excipients are suitable for use by ascertaining what the appropriate good manufacturing practice is.

In the scope of human medicinal products, apart from regular supervision of active substance manufacturers, importers and distributors on its own territory, the Competent Authority may carry out inspections at manufacturers or distributors of active substance(s) in third countries as well as at manufacturers or importers of excipient(s) in their own Member State and in third countries whenever it has grounds for suspecting non-compliance.

In the scope of veterinary medicinal products, the Competent Authority may carry out inspections at manufacturers of active substance(s) in third countries as well as in their own Member State whenever it has grounds for suspecting non-compliance.

Article 46(f) of Directive 2001/83/EC and Article 93 (1) (j) of Regulation 2019/6 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 active substances. The holder of the manufacturing authorisation for human medicinal products shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47 of Directive 2001/83/EC.

When an application for a marketing authorisation for human medicinal product, or variation to change or add a new active substance manufacturer, is submitted, the applicant is expected to include a declaration by the Qualified Person(s) of the manufacturing authorisation holder(s) that the active substance(s) concerned is/are manufactured in accordance with the detailed guidelines on good manufacturing practice for active substances (Article 8(3) (ha) of Directive 2001/83/EC).

It is mandatory for human medicinal products and expected for veterinary medicinal products 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 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 93 (1) (j) of Regulation 2019/6, regulatory action may be taken against the manufacturing authorisation holder and where necessary, appropriate action in connection with products on the market.

## 5. Supervisory authority

Supervisory authority for active substance manufacturing sites located in the EEA is the authority of the country where the site is located. For active substance manufacturing sites located in countries outside the EEA, a Member State which is the supervisory authority for a medicinal product has also the responsibility for supervision and inspection of the active substance manufacturers associated with the medicinal product.

Member States have responsibility for verifying GMP compliance of active substance manufacturing sites in the following cases:

Figure: 1. Active substance manufacturers located in their territory

Figure: 1. Active substance manufacturers located in a third country, supplying finished product manufacturers located in the member state in question.

Figure: 2. Active substance manufacturers located in a third country, supplying finished product manufacturers located in the same or another third country, which then subsequently supply finished product (or finished product intermediates) to an importer in the member state in question.

## 6. Examples of inspection triggers

The following is a list of examples of when an inspection of premises of manufacturers, importers and distributors of starting material, which is, in turn, used in the manufacture of a human or veterinary medicinal product, may be required. Please note that many of the following examples do not apply for starting materials (especially not for excipients) used in the manufacture of veterinary medicinal products as the Regulation 2019/6 doesn't require that guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients shall adopted.

The legislation provides for unannounced inspections but this is not expected to become a routine practice. Member States are expected to reserve unannounced inspections for occasions where such action is appropriate.

(Reference to Directive 2001/83/EC / Regulation 2019/6; if there is only one reference quoted, it refers to Directive 2001/83/EC).

- 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 applications for variations to existing marketing authorisations (Article 19(1)/ Article 28 (1) of Regulation 2019/6)

- The competent authority may carry out an inspection during the registration process of manufacturers, importers and distributors of active substances which are located in their own territory (Article 52a (4) of Directive 2001/83/EC and Article 95 (4) of Regulation 2019/6).
- Inspections and an effective follow-up thereof should be carried out at an appropriate frequency based on risk at the premises of the manufacturers, importers, or distributors of active substances, located in the EEA by the competent authority of each Member State on its own territory (Article 111(1b) of Directive 2001/83/EC and Article 123 (3) of Regulation 2019/6).
- When there are grounds (e.g. based upon receipt of information from any Competent Authority inside or outside the EEA, in certain cases by anonymous sources) for suspecting non-compliance with the legal requirements laid down in Directive 2001/83/EC and Regulation 2019/6, inspections may be carried out at the premises of manufacturers of active substances, distributors of active substances as well as importers of active substances located in the EEA and third countries (Article 111(1b) of Directive 2001/83/EC and Article 123 (3) of Regulation 2019/6). Manufacturers of excipients inside the EEA and 3<sup>rd</sup> countries and importers of excipients in the EEA can be inspected for the same reasons if these starting materials are intended to be used for medicinal products for human use.

Examples (non-exhaustive):

Figure: 1. When there is non-compliance with the principles and guidelines of good manufacturing practice of active substances. This may include invocation of the safeguard clause contained in an 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.

Figure: 1. When analysis of a sample of starting material carried out by, or on behalf of, the competent authority indicates significant non-compliance with the specification.

Figure: 1. When a report of a serious adverse reaction and/or recall of a medicinal product in which the quality of the active substance is implicated has to be followed.

Figure: 2. 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.

Figure: 3. 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

Figure: 4. When recommended in an inspection report as a consequence of, or follow up to, observations from another inspection.

Figure: 5. 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.

Figure: 6. When an exceptional impact has been identified after a risk-assessment (e.g. Compilation procedure 'A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers')

Figure: 1. when- without prejudice to additional national requirements (manufacturing authorisation) - 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 of medicinal products.).

Figure: 2. when any other high intrinsic risk (reflecting the complexity of the site, its processes and products as well as the criticality of the products or services provided by the site including from a supply perspective) or high compliance risk (reflecting the GMP-compliance status of the site immediately following the most recent routine inspection at the site) has been identified related to the manufacturing, importation and distribution of active substances or manufacturing and importation of excipients.

- When there is neither a “written confirmation” according to Article 46b(2b) of Directive 2001/83/EC for an active substance that is intended to be imported, nor the exporting country is on the “white list” according to Article 111b and when it is necessary to ensure the availability of the human medicinal product(s) that is/are manufactured by using this active substance (use of waiver in Article 46b(4) of Directive 2001/83/EC).
- When requested by another Member State where the requesting authority provides a written request detailing why an inspection is necessary (Article 111(1c) of Directive 2001/83/EC /Article 123 (4) of Regulation 2019/6)
- When requested by the European Commission where the Commission provides a written request detailing why an inspection is necessary (e.g. shortage) (Article 111(1c) of Directive 2001/83/EC/Article 123 (4)of Regulation 2019/6)
- When requested by the European Medicines Agency (EMA) in relation to the assessment of a product under the centralised system or in connection with matters referred to it in accordance with Union legislation (Article 111(1c) of Directive 2001/83/EC / Article 123 (4) of Regulation 2019/6)
- When requested by the Commission or the EMA 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.), or when the EDQM suspects that there are grounds for suspending or withdrawing a conformity certificate (Article 111 (1e) of Directive 2001/83/EC / Article 125 of Regulation 2019/6) (Res AP/CSP (07)1)
- Where there is disagreement between Member States on the conclusions from an inspection (Article 122(3) of Directive 2001/83/EC). For veterinary products in the absence of a specific legal basis in Regulation 2019/6, the national competent authorities have agreed to follow the principles of the same arbitration procedure set out in article 122 of Directive 2001/83/EC for human medicinal products.
- Where an uninvolved Member State is requested by the Commission to participate in a re-inspection in another Member State in case of divergent opinions (Article 122(3) of Directive 2001/83/EC / Article 82 of Regulation 2019/6)
- When requested by a manufacturer of starting materials (e.g. an active substance or excipient), which is located in their Member State or in a non-EEA and non-MRA country dependent on the resources and other priorities of the Member State concerned. There is no guarantee that the national competent authority will fulfil the inspection request. In the case of a third country active substance manufacturer, 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. Where a manufacturer of active substances or excipients supplies to a number of manufacturing authorisation holders in two or more Member States, the choice of the competent authority to carry out the inspection is left to that active substance manufacturer.

# The issue and update of GMP certificates

## Table of contents:

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4. Non-compliance with GMP
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<b>Title</b>	<b>The issue and update of GMP</b>
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Notes	GMP Certificates are issued, where appropriate, to manufacturers following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC and 94 (1) of Regulation 2019/6. They are also entered into the Union database (EudraGMDP) as required in Arts 111(6) of Directive 2001/83/EC and 91 (3) of Regulation 2019/6.

# The Issue and Update of GMP Certificates

## 1. Introduction

Art. 111 (5) of Directive 2001/83/EC and Art. 94 (1) of Regulation 2019/6as 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 European Union law. The GMP certificates issued, or the information indicating that a manufacturer does not comply, shall be entered into the EudraGMDP database.

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.

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 the overall conclusion of an inspection with respect to compliance with GMP. In some cases, normally for sites 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. GMP certificates may be verified using the EudraGMDP database.

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.

## 3. When GMP Certificates should be issued and EudraGMDP entry

### 3.1 Responsibility for issue of GMP Certificates

For medicinal products responsibility for issuing GMP certificates and placing entries into EudraGMDP rests with the supervisory authority, including those certificates issued following inspections performed at the request of the Commission, EMA, EDQM, Member State or an active substance manufacturer. If more than one authority carries out an inspection of a third country manufacturer then these authorities should agree on who will take on this responsibility for issuing the certificate.

Following each relevant inspection, a report in accordance with the Union 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 European Union legislation. Where this is the case, within 90 days of the last day

of the inspection concerned, the authority should issue a GMP certificate in accordance with the Union format to the manufacturer that underwent the inspection. In the case of non-compliance see the relevant Union 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.

Hard copy 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, but all parties should be encouraged to use EudraGMDP wherever possible

### 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) are as follows:

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 short period of time after the first visit 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.

Depending on national legislation, paper GMP certificates need not be issued to manufacturers of investigational medicinal products. Nevertheless EudraGMDP entry is 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 Union procedures.

Inspections may be 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 EudraGMDP database contains a drop down menu but the certificate should include free text sufficiently explaining the reasons for the restriction. See also section 4.

### 3.4 Responsibility for EudraGMDP database entry

The authority performing the inspection is responsible for entering the details of the certificate into EudraGMDP within 90 days of the relevant inspection.

### 3.5 EudraGMDP entry for GMP Certificates issued by MRA Partners

MRA partners are encouraged to use GMP Certificates uploaded into EudraGMDP by EEA authorities rather than request paper versions. Similarly, they are authorised to upload

certificates themselves upon the request of EEA authorities or local manufacturer for the purposes of the MRAs.

### 3.6 Investigational Medicinal Products for Human Use (IMPs)

Directive 2001/83/EC or Regulation 536/2004 do 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. It has been agreed that the appropriate database is EudraGMDP database for GMP inspections of manufacturers of IMPs.

### 3.7 Investigational Medicinal Products for Veterinary Use (VIMPs)

Regulation 2019/06 does not make reference to the issue of GMP certificates following an inspection of a manufacturer of veterinary IMPs, however Member States may choose to do so, in order to facilitate the exchange of information on clinical trials. It has been agreed that the appropriate database is EudraGMDP database for GMP inspections of manufacturers of IMPs.

## 4. Non-compliance with GMP

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

## 5. Renewal and update of GMP Certificates<sup>1</sup>

5.1 A certificate itself is not normally 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 EudraGMDP however require a different approach.

EudraGMDP 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 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.

It may not always be appropriate to withdraw existing information that 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:

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<sup>1</sup> Due to the ongoing COVID-19 public health emergency and subsequent restrictions on EU inspectorates an automatic extension of the validity date of GMP certificates was agreed by GMDP IWG.

- 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 EudraGMDP 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.

## 5.3 GMP certificate validity periods

### 5.3.1 Initial validity period

A GMP certificate reflects the status of the manufacturing site at the time of the inspection. It should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, unless extended by the issuing authority.

On the basis of inspection outcome and risk evaluation, the issuing authority may condition a GMP certificate to give a specific validity of less than three years by an entry in the Restrictions or Clarifying remarks field. In this case, the validity period may not be extended. A re-inspection may (with the exception of active substances, where permitted by the national competent authority) be performed by the issuing authority within the required timeframe indicated by the restriction.

### 5.3.2 Extension of GMP certificate validity period

GMP certificates may continue to be used for the period extended by the issuing authority. They may not be used to support regulatory applications beyond the stated validity period. A GMP certificate which was not initially restricted in respect of validity period may be extended if a re-inspection is not performed within the three year timeframe. The extension of validity may be up to a maximum of:

- a further two years for manufacturers located in the EEA and for manufacturers located in Third Countries (i.e. total of five years from date of inspection)

Extensions of GMPc validity period should not lead to changes in the scope (buildings, lines or manufacturing activity) of the certificate.

The decision to extend the validity period should be based on a GMP compliance risk assessment of relevant factors by the issuing authority. This may include, but not be limited to, those requirements listed in the Annex to the "Outline of a Procedure for Coordinating the verification of the GMP status of Manufacturers in Third Countries" SOP.

GMP certificates should be extended by issuing a new certificate with reference to the previous inspection date. This provides traceability to previous versions.

An extended certificate must include a conditioning remark on the GMP certificate and, for sites located in a third country, an update to the EudraGMDP inspection planning module, to indicate the next scheduled inspection date and scope.

- The following conditioning text should be used in the Restrictions or Clarifying remarks field of the GMP certificate:

*"Following a risk-based review of GMP compliance information conducted on [date of review], the validity period of this certificate is extended to [new date of expiry]."*

- GMP certificates extended for third country manufacturers should **also** include the following text:

*"National Competent Authorities may view future inspection scheduling in the EudraGMDP planning module"*

#### 5.3.3 Change in EU supervisory authority of a third country manufacturer when extending GMP certificate validity period

A third country manufacturer may change its supervisory authority (SA) between inspections. In this case, if GMP certificate extension is required before re-inspection by the new SA, both authorities have shared responsibilities.

The desktop compliance review and decision to extend the GMP certificate validity period must be performed by the SA that issued the original certificate.

The new SA is responsible for entering information in EudraGMDP planning module and performing the next inspection.

Communication between both authorities is important to ensure re-inspection scheduling which is compatible with the compliance assessment and extension of certificate validity.

#### 5.3.4 Validity period of GMP certificates or compliance documents following remote review of information

If a GMP certificate (or equivalent document(s)) has been issued by a SA following a review of compliance information from trusted regulatory partners or 'distant assessment' procedure, it should not be extended beyond three years. A new (full) assessment or inspection should be performed.

## 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 EudraGMDP database along with any manufacturing authorisation and non-compliance information.

# A model for risk based planning for inspections of pharmaceutical manufacturers

## Table of contents:

1. Introduction
2. Purpose
3. Scope
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5. How to use this quality risk management tool
6. Revision history
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<b>Title</b>	<b>A model for risk based planning for inspections of pharmaceutical manufacturers</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable



# A model for risk based planning for inspections of pharmaceutical manufacturers

## 1. Introduction

- 1.1. According to Directive 2001/83/EC and Regulations 536/2014 and 2019/6, respectively, the Competent Authority shall ensure, by means of 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 and supervision 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.
- 1.5. This document sets out a simple and flexible Quality Risk Management tool that may be used by GMP Pharmaceutical Inspectorates when planning the frequency and scope of GMP inspections. It is a methodology that is based upon the concept of rating manufacturing sites on the basis of an estimated risk that they may pose to patients, consumers, animals and users of medicines. The methodology also takes into account the risk to product quality.
- 1.6. The methodology provides a simple two-page quality risk management worksheet that is designed to be completed by Inspectors immediately following an inspection at the site. The worksheet is presented in Appendix 1 to this document and is designed to not require more than several minutes to complete.
- 1.7. This Quality Risk Management tool was designed in line with the principles, concepts and guidance set out in the following official documents:

Figure: 1. PI-37-1- A Recommended Model for Risk-based Inspection Planning in the GMP Environment;

Figure: 2. ICH Q9 - Quality Risk Management;

Figure: 3. Annex 20 to the PIC/S GMP Guide;

Figure: 4. ICH Q10 – Pharmaceutical Quality Systems.

## 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. The purpose of this document is to provide a simple and qualitative Quality Risk Management tool that may be of use to GMP Pharmaceutical Inspectorates to prioritise sites for inspections when planning the frequency and scope of GMP inspections.

## 3. Scope

3.1. The scope of this document covers the following:

Figure: 1. The planning of routine GMP inspections of active substance and medicinal product manufacturers by the Competent Authorities of the Member States;

Figure: 2. Domestic and third country manufacturers;

Figure: 3. The planning of routine GMP inspections of Investigational Medicinal Product (IMP) manufacturers by the Competent Authorities of the Member States;

Figure: 4. Follow-up activities, such as assigning a new risk rating to the site following the receipt of new information about the site or its products. (Note: this normally occurs between inspections and the types of new information might include information on quality defects, product recalls, market surveillance test results, etc.);

Figure: 5. Note: While this methodology has not been designed for the planning of GDP inspection programmes or for the planning of inspections at pharmacies, some countries may choose to use it as a basis for those purposes and it may be of help in those areas.

3.2. The scope of this document does not extend to the following:

Figure: 6. The actual conduct of an inspection;

Figure: 7. The planning of inspections at new manufacturers before any inspection has taken place;

Figure: 8. This methodology requires knowledge of the GMP compliance status of the site. It is considered that new sites should not be rated for their initial inspection in accordance with this Quality Risk Management tool, because the GMP Pharmaceutical Inspectorate in question will not likely have sufficient knowledge about the site to assign a risk rating to that site. (However, certain aspects of this methodology, such as the intrinsic risk evaluation, may be useful to apply to new sites when planning inspections at new sites.);

Figure: 9. The planning of non-routine and emergency inspections at manufacturers, such as when a Critical deficiency or many Major deficiencies have been identified during a recent inspection;

Figure: 10.

Figure: 11. It is usually not necessary or indeed helpful to use a formal Quality Risk management methodology such as this one to determine whether a non-routine or emergency inspection should be performed;

Figure: 12. The planning of for-cause inspections that must be carried in order to approve or reject a variation application to a Marketing or Manufacturing Authorisation;

Figure: 13. The methodology presented in this document was not designed to apply to the inspection of blood and tissue establishments, but it may be modified for application in this area;

Figure: 14. This Quality Risk Management tool should not normally be applied to a site until a full inspection at the site has occurred. This is because the compliance status of the site needs to be determined in order to use this tool;

Figure: 15. If a site has had one initial inspection but if the GMP Pharmaceutical Inspectorate in question considers that this initial inspection was not a 'full' inspection of the site and that one or more additional inspections are required before the site can be considered to have had a 'full' inspection, such sites should not be rated using this Quality Risk Management tool until they have been subjected to a 'full' inspection;

Figure: 16. A useful rule of thumb to use is that the tool should not be applied to a site until the site has been granted a Manufacturing Authorisation and/or a GMP Certificate, as these actions indicate that the site will have been assessed from a compliance perspective;

Figure: 17. This procedure covers both human and veterinary medicinal products.

## 4. Procedure

### 4.1. Principle

Planning and scheduling of inspections is realised as follows:

Figure: 18. Complete the worksheet presented in Appendix 1 to this document immediately following an inspection at the site.

- Assign risk ranking (based on an intrinsic risk and a compliance-related risk) for each site;
- Establish the recommended inspection frequency;
- Establish the recommended scope of the next routine inspection.

Figure: 19. Establish the necessary expenditure of inspection time for each site (see Appendix 3);

Figure: 20. Update the frequency and/or scope of the next routine inspection as new information on the compliance status of the site or on its activities and products is received;

Figure: 21. In the case of manufacturing sites in third countries, this information should be put in EudraGMDP planning module.

4.2. This Quality Risk Management methodology is a simple tool that allows GMP Pharmaceutical Inspectorates to assign a relative risk rating to manufacturers when planning the routine inspection programme for those sites.

4.3. The risk ratings that are generated using this methodology may be used by the GMP Pharmaceutical Inspectorate to assign a frequency to the routine inspections that will be performed at the various manufacturers under its supervision.

- 4.4. The scope of an inspection may be general and cover the full range of activities at the site, or may be limited to specific activities. Where the latter approach is used, the Competent Authority should ensure that all relevant critical activities are covered within a 5 year period.
- 4.5. Generally the interval between inspections by trusted authorities<sup>1</sup> 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 (non-routine) inspections e.g. due to product quality defects or significant changes of building, equipment or processes is not affected. This methodology is not designed to be used to determine when such non-routine inspection should occur, as there is usually no need to use a formal tool such as this one to decide when such an inspection should occur.
- 4.6. The risk ratings that are assigned to sites are based on an assessment of two different kinds of risk - an intrinsic risk and a compliance-related risk.
- 4.7. The intrinsic risk estimated for a site reflects the complexity of the site, its processes and products as well as the criticality of the products or services provided by the site including from a supply perspective. These items (complexity and criticality) usually remain fairly constant regardless of the compliance status of the site. Therefore, one usually cannot estimate this risk on the basis of inspection deficiencies or compliance history.
- 4.8. The compliance-related risk that is estimated for the site reflects the GMP compliance status of the site immediately following the most recent routine inspection at the site. When this risk is being estimated, the classification and number of deficiencies identified at the last inspection are taken into account.
- 4.9. Note: Guidance on how to assess the intrinsic risk is provided in Appendix 2. This is important to read before using the tool. A table is provided in the worksheet (Appendix 1) showing how to assess the compliance-related risk.
- 4.10. Once the intrinsic risk and the compliance-related risk associated with the site have been estimated, those two risks are then combined using a simple matrix to generate a relative risk rating for the site. It is this risk rating that is considered when deciding the frequency of the next routine inspection at the site.
- 4.11. To define the scope and date of the next inspection of the manufacturing site, the Competent Authority should also take into account the following factors:
  - 4.11.1 Agency's knowledge of the company (overall compliance status and history of the company and facility).
  - 4.11.2 Results of product testing by OMCL's.
  - 4.11.3 Number and significance of quality defects (e.g. recall).
  - 4.11.4 Marketing Authorisation variations affecting the site.
  - 4.11.5 A failure to implement a Marketing Authorisation variation on time.
  - 4.11.6 Compliance information from trusted authorities outside the EU.

The main pre-requisites for consideration of compliance information from international partners are:

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<sup>1</sup> Please see 4.11.6. for a definition of 'trusted authorities'.

Figure: 1. The manufacturer has already undergone a full inspection by an EU/EEA Competent Authority in the past;

Figure: 2. The received compliance information is sufficient to enable the assessment of the GMP compliance of the site;

Figure: 3. An authority can be considered as 'trusted' when there is a high degree of similarity between the EEA's and the authority's inspection procedures and GMP standards (currently equivalent inspections can be considered in connection with an MRA, AACA and PIC/S).

Guidance on the delay of a re-inspection of a manufacturer based on the inspectorate's assessment of the intrinsic and compliance-related risks and compliance information from a trusted authority is provided in Appendix 4.

4.11.7 Major changes of building, equipment, processes, personnel.

4.11.8 Experience with manufacturing of a product (e.g. frequency, volume, number of batches).

4.12. With regard to the scope of the next routine inspection at the site, this is not determined using the risk rating that is assigned to the site. Instead, this Quality Risk Management methodology requires certain other items to be considered when the recommended scope of the next inspection is being documented.

These other items are:

4.12.1 The required focus and depth of the next routine inspection of the site.

4.12.1 The required duration of the next routine inspection of the site.

4.12.1 The required number of inspectors to be assigned to the next routine inspection of the site.

4.12.1 Whether any specific competence or expertise will be required on the inspection team when performing the next routine inspection of the site.

4.13. When determining the required focus and depth of the next routine inspection, the methodology requires the inspector to consider the following items before making his/her recommendation:

4.13.1 The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies.

4.13.1 The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site.

4.13.1 The areas that were considered during the last inspection to have been inadequately resourced at the site.

4.13.1 Any other area that the inspector feels requires detailed review at the next inspection.

4.14. The recommended scope of the next routine inspection is documented on the worksheet after the last inspection has been performed at the site. The person who should do this will normally be the inspector who led the last inspection at the site in question. (This approach is advantageous because it utilises the existing knowledge of the inspector who most recently inspected the site.)

4.15. Expenditure of time

Appendix 3 gives guidance values for the required inspection time per type of site. The time spent on the site may be adjusted in accordance with the national re-inspection programmes of the Competent Authorities. The type of manufacturing site is classified by the relevant dosage form and the manufacturing process, respectively.

The required time may be adjusted accordingly, depending on these factors:

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

4.16. This methodology recognises that new information on the compliance status of the site or on its activities and products may be received by the Inspectorate after the site has been rated using this methodology to determine the frequency of the next routine inspection, and after the scope of the next routine inspection has been documented.

4.17. This methodology also recognises that changes made (or proposed to be made) at a site may trigger a non-routine inspection at the site. Again, as stated above, this methodology is not designed to be used to determine when such non-routine inspection should occur, as there is usually no need to use a formal tool such as this one to decide when such an inspection should occur.

4.18. 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 following this procedure and is documented in the worksheet (Annex 1).

4.19. 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.

## 5. How to Use This Quality Risk Management Tool

5.1. When using this Quality Risk Management tool, a two-page worksheet document needs to be completed for each site that is being rated. The format of this worksheet is shown in Appendix This worksheet contains seven parts, A through G.

### 5.2. Part A of the Quality Risk Management tool worksheet – Preliminary Information

Part A is where preliminary information about the site is documented. This includes the site name and address, the authorisation numbers held by the site, etc.

### 5.3. Part B of the Quality Risk Management tool worksheet – Intrinsic Risk

Part B is where the intrinsic risk associated with the site is estimated. There are two risk-indicating factors that need to be considered here – the complexity of the site, its processes and products, and the criticality of the products manufactured by the site (or the criticality of the services provided by the site, such as contract analytical testing services).

Appendix 2 provides detailed guidance on the meaning of each of these items (Complexity and Criticality) and on how to score each.

A score of 1, 2 or 3 is assigned to the Complexity factor and this is documented on the worksheet in Part B. (A complexity of 3 represents a high complexity; a complexity of 1 represents a low complexity.)

A score of 1, 2 or 3 is assigned to the Criticality factor and this is documented on the worksheet in Part B. (A complexity of 3 represents a high Criticality; a complexity of 1 represents a low Criticality.)

A Matrix, table, shown in Table 1 below, is provided on the worksheet for combining these two scores to generate an estimate of the Intrinsic risk associated with the site, and this is also documented in Part B.

	Criticality		
Complexity	1	2	3
1	1 (Low)	2 (Low)	3 (Medium)
2	2 (Low)	4 (Medium)	6 (High)
3	3 (Medium)	6 (High)	9 (High)

Table 1: Intrinsic Risk Matrix

A total score of 1 or 2 represents a Low Intrinsic Risk

A total score of 3 or 4 represents a Medium Intrinsic Risk

A total score of 6 or 9 represents a High Intrinsic Risk

### 5.4. Part C of the Quality Risk Management tool worksheet – Compliance Risk

Part C is where the *compliance-related risk* associated with the site is estimated and documented. This is solely based on the deficiencies identified at the last inspection of the site. (Note: If the last inspection was not a routine or a full inspection, the deficiencies identified at the last routine (or full)

inspection as well as those identified at the last non-routine inspection should be taken into account when scoring this risk).

The following table is provided as guidance when scoring the *compliance-related risk* associated with the site. The contents of this table may be customised to reflect the policy of the Inspectorate using this methodology.

2. Deficiency Profile	3. Compliance-related Risk Score
a. or more Critical	5. High
6. From 1 to 5 Major Deficiencies	7. Medium
8. No Major or Critical Deficiencies	9. Low

Table 2: Compliance Risk Table

A score of High, Medium or Low is assigned to the *compliance-related risk* associated with the site, and this is documented on the worksheet in Part C.

It is recognised that sites with a High Compliance-related Risk Score may need to be inspected again very soon after the inspection that identified the poor state of compliance. Such sites may also be directed to cease production and they may have their manufacturing licence revoked or varied until they demonstrate a satisfactory level of compliance during a follow-up inspection.

In this regard, it is important to note the following:

- Such follow-up inspections are by definition non-routine. They are also sometimes referred to as 'for-cause' or 'emergency' inspections and they may occur when a site has had a Critical or many Major deficiencies (e.g. 6 or more Majors) identified;
- When a site warrants such a follow-up inspection, (e.g. within 3 months of the previous inspection), the use of this Quality Risk Management tool should be suspended until after the for-cause inspection, at which time the routine inspection programme will likely restart for the site. In practice, this can mean that, when a site has been given a Critical or a large number of Major deficiencies, (e.g. 6 or more), and if a follow-up for-cause inspection is planned in response to those deficiencies, the GMP Pharmaceutical Inspectorate should only apply this tool to the site again after the for-cause follow-up inspection has been completed and the routine inspection programme restarted;
- When resuming use of this tool in relation to the site in question, the Compliance Risk Score assigned to the site should be based on the deficiencies identified during the initial problematic inspection (i.e. the one with the Critical or the many Major deficiencies) as well as any deficiencies identified during the follow-up inspection;

#### 5.5. Part D of the Quality Risk Management tool worksheet – Overall Risk Rating

Part D is where the intrinsic risk and the compliance-related risk associated with the site are combined to generate the overall risk rating for the site.

A simple matrix, as shown in Table 3 below, is provided on the worksheet for generating this risk rating, and the resulting risk rating is documented in Part D of the Worksheet.

10.	11. Intrinsic Risk		
12. Compliance Risk	13. Low	14. Medium	15. High



16. Low	17. Risk Rating = A	18. Risk Rating = A	19. Risk Rating = B
20. Medium	21. Risk Rating = A	22. Risk Rating = B	23. Risk Rating = C
24. High	25. Risk Rating = B	26. Risk Rating = C	27. Risk Rating = C

Table 3: Risk Rating Matrix

There are three possible risk ratings, A, B & C. ('A' represents a relatively low risk site and 'C' represents a relatively high risk site).

5.6. Part E of the Quality Risk Management tool worksheet – Inspection Frequency

Part E is where the risk rating from Part D is used to generate and document the recommended frequency for routine inspections at the site.

Sites with an 'A' Risk Rating have at least one Low risk score for Intrinsic risk or for Compliance risk. During routine inspection programmes, these sites may be inspected at a reduced frequency, for example, at a frequency less than every two years (e.g. one inspection every 2.5 years);

Sites with a 'C' Risk Rating have at least one High risk score for Intrinsic or for Compliance risk. During routine inspection programmes, these sites may be inspected at an increased frequency, for example, at least annually or even more frequently;

Sites with a 'B' Risk Rating lie in-between and during routine inspection programmes, these sites may be inspected at an intermediate frequency, for example, between 12 and 24 months.

Table 4 below shows one possible way of assigning inspection frequencies based on the Risk Rating. Other approaches may also be used.

28. Risk Rating	29. Suggested Inspection Frequency
30. A	31. Reduced Frequency, 2 to 3 yrs
32. B	33. Moderate Frequency, 1 to 2 yrs
34. C	35. Increased Frequency, < 1 yr

Table 4: Suggested Inspection Frequency for Each Risk Rating

**Note 1:** The above Risk Rating matrix is designed so that no site with a High Intrinsic Risk score or a High Compliance Risk score is assigned a reduced inspection frequency. This is because it is considered wise to adopt a policy of inspecting all sites with a high intrinsic or compliance risk rating at least once every two years during routine inspection programmes. However, when a site has been given a High Compliance Risk score, as noted above in Section 7.1.3, a non-routine, for-cause inspection may be required at the site, and this has implications for the use of this tool during that time. See Section 5.1.3 for further details.

**Note 2:** It is important to note that the inspection frequencies shown in Table 4 above are presented in terms of time range intervals, not absolute time intervals.

For example, for sites assigned a 'B' Risk Rating, the time range for the inspection frequency is set out at 1-2 years; it is not an absolute 2 years;

The actual inspection frequency assigned to a site within any one Risk Rating (A, B or C) should reflect the number and type of deficiencies that were identified during the last inspection;

For example, if two sites are assigned a Risk Rating of B, but if one of the sites had a poorer last inspection outcome than the other (e.g. five Major deficiencies versus one Major) the exact inspection

frequency assigned to the former site should generally be towards the more restrictive end of the time range (i.e. an inspection frequency closer to one year than to two years);

In addition, the inspection frequencies assigned to sites that have the same Risk Ratings may take into account the individual scores for the intrinsic and compliance risks. For example, when a site has both a High Intrinsic Risk and a High Compliance Risk, resulting in an overall Risk Rating of C, the assigned inspection frequency (e.g. 9 months) may be higher than that assigned to a site which has a High Intrinsic Risk but a Medium Compliance Risk, which also results in an overall Risk Rating of C;

**Note 3:** In some cases, the Inspector(s) who last inspected a site may disagree with the inspection frequency that is assigned to that site using this methodology.

If this occurs and if the Inspector(s) believe that a different Inspection frequency should be assigned to the site, the reasons for this should be formally documented. Factors which may be useful to consider here are:

- The robustness of the Quality Management System, including its approach to Quality Risk Management;
- The general GMP compliance history of the site, taking into account recurring non-compliance issues and failures to address deficiencies following inspections in a satisfactory manner;
- Significant failures to address previous GMP deficiencies.

Recognising that the outcomes of Quality Risk Management work can be subjective and uncertain, the Inspector's views may modify the inspection frequency assigned by this methodology;

However, each Inspectorate may wish to adopt its own approach when such situations arise, and those approaches may differ from that presented above.

#### *5.7. Part F of the Quality Risk Management tool worksheet – Inspection Scope*

Part F is where the recommended scope of the next routine inspection is documented. This Part should be completed either immediately after the inspection, or once the inspection report has been issued, and ideally at the same time as the previous sections.

There are four sections to complete in Part F, as follows:

- The required focus and depth of the next routine inspection of the site;
- The required duration of the next routine inspection of the site;
- The required number of inspectors to be assigned to the next routine inspection of the site;
- Whether any specific competence or expertise will be required on the inspection team when performing the next routine inspection of the site.

Once Parts E and F have been completed, the recommended frequency and scope of the next routine inspection will have been documented on the worksheet. It is anticipated that the inspection planning staff at the GMP Pharmaceutical Inspectorate in question may then use this information when planning the routine inspection programme for the manufacturing sites under their supervision.

### 5.8. Part G of the Quality Risk Management tool worksheet – Who & When

Part G is where the names of the persons that have completed the Quality Risk Management exercise are documented, and the signature (and date) of the person who completed the worksheet form is also recorded here.

Reviewing and Updating the Quality Risk Management exercises as required

The outputs of Quality Risk Management exercises performed using this methodology should be reviewed when new information becomes available to the Inspectorate that may change the risk profile of a site.

Such new information may arise from quality defect issues, recalls, market surveillance test results, assessment findings, enforcement investigations, site changes, etc;

In addition, variations to Marketing or Manufacturing Authorisations may mean that the activities of a site are to expand or change substantially. For example, an MA variation to switch from glass to plastic ampoules as the primary packaging component for a product may require the introduction of blow-fill-seal technology at the manufacturing site. Such MA variations may change the complexity or criticality associated with the site and, for the purposes of this methodology, such variations may be regarded as new information about the site;

Significant changes in the number of personnel at a site are also useful to consider from a risk perspective during the review phases, because such changes may indicate a change in the complexity of the site, thus possibly affecting the intrinsic risk, or, they may mean that there are fewer QA resources available at the site, which could lead to compliance problems later on;

Also, the company's response report following the most recent inspection report should be considered as new information and is useful to review during this stage of applying this methodology. This is because the Inspector who reviews the company's response report may decide that there are specific aspects relating to the responses that need to be closely followed up on during the next inspection; this may thus warrant an expansion in the scope of the next routine inspection.

The above types of new information may warrant not only a change in the recommended scope of the next routine inspection, they may also require a change in the recommended frequency of the next routine inspection. It is left up to each individual Inspectorate to manage how the Quality Risk Management exercise pertaining to an individual site should be updated upon receipt of new information about the site.

It is recommended that these Quality Risk Management exercises be subjected to formal periodic review.

## 6. Revision History

Date	Version Number	Reasons for revision

\*\*\*\*\*

**Appendix 1: The Worksheet used by this Quality Risk Management Tool**

PART A – Preliminary Information about the Site																							
<b>Site Name</b>																							
<b>Site Address</b>																							
<b>Licence Number (if any)</b>																							
<b>FP or API Manufacturer?</b>																							
<b>Last Inspection Date</b>																							
<b>Name of previous lead Inspector</b>																							
PART B – The Intrinsic Risk Associated with the Site																							
Risk Factor	Risk Score	Matrix for Estimating the Intrinsic Risk																					
The Complexity of the site, its processes and products, is regarded as:	<b>1   2   3</b> <b>Circle one</b>	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr style="background-color: #d3d3d3;"> <th colspan="4">Criticality</th> </tr> <tr style="background-color: #d3d3d3;"> <th>Complexity</th> <th>1</th> <th>2</th> <th>3</th> </tr> </thead> <tbody> <tr> <td style="background-color: #d3d3d3;">1</td> <td>1 (Low)</td> <td>2 (Low)</td> <td>3 (Med)</td> </tr> <tr> <td style="background-color: #d3d3d3;">2</td> <td>2 (Low)</td> <td>4 (Med)</td> <td>6 (High)</td> </tr> <tr> <td style="background-color: #d3d3d3;">3</td> <td>3 (Med)</td> <td>6 (High)</td> <td>9 (High)</td> </tr> </tbody> </table>		Criticality				Complexity	1	2	3	1	1 (Low)	2 (Low)	3 (Med)	2	2 (Low)	4 (Med)	6 (High)	3	3 (Med)	6 (High)	9 (High)
Criticality																							
Complexity	1	2	3																				
1	1 (Low)	2 (Low)	3 (Med)																				
2	2 (Low)	4 (Med)	6 (High)																				
3	3 (Med)	6 (High)	9 (High)																				
The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:	<b>1   2   3</b> <b>Circle one</b>	<p><b>Use the above matrix and record the Intrinsic Risk associated with the site below:</b></p> <p style="text-align: center;"> <b>Low</b> <input type="checkbox"/>    <b>Medium</b> <input type="checkbox"/>    <b>High</b> <input type="checkbox"/> </p>																					
PART C – The Compliance-related Risk based on the last Inspection																							
The <b>compliance risk</b> indicated by the most recent deficiency profile of the site is:	<b>Low</b> <input type="checkbox"/> <b>Medium</b> <input type="checkbox"/> <b>High</b> <input type="checkbox"/>	<ul style="list-style-type: none"> <li>- No Major or Critical Deficiencies</li> <li>- 1 to 5 Major Deficiencies: Number of Majors =</li> <li>- 1 or more Critical Deficiencies or more than 5 Majors</li> </ul> <p style="text-align: center;">(Note: Customise as appropriate)</p>																					
PART D – The Risk-Rating assigned to the Site																							
Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the <b>Risk Rating</b> for the site.																							
<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr style="background-color: #d3d3d3;"> <th colspan="4">Intrinsic Risk</th> </tr> <tr style="background-color: #d3d3d3;"> <th>Compliance Risk</th> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td style="background-color: #d3d3d3;">Low</td> <td>Risk Rating = A</td> <td>Risk Rating = A</td> <td>Risk Rating = B</td> </tr> <tr> <td style="background-color: #d3d3d3;">Medium</td> <td>Risk Rating = A</td> <td>Risk Rating = B</td> <td>Risk Rating = C</td> </tr> <tr> <td style="background-color: #d3d3d3;">High</td> <td>Risk Rating = B</td> <td>Risk Rating = C</td> <td>Risk Rating = C</td> </tr> </tbody> </table>				Intrinsic Risk				Compliance Risk	Low	Medium	High	Low	Risk Rating = A	Risk Rating = A	Risk Rating = B	Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C	High	Risk Rating = B	Risk Rating = C	Risk Rating = C
Intrinsic Risk																							
Compliance Risk	Low	Medium	High																				
Low	Risk Rating = A	Risk Rating = A	Risk Rating = B																				
Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C																				
High	Risk Rating = B	Risk Rating = C	Risk Rating = C																				
<b>The Risk Rating associated with this site is: A</b> <input type="checkbox"/> <b>B</b> <input type="checkbox"/> <b>C</b> <input type="checkbox"/>																							
PART E – The Recommended Frequency for Routine Inspections at the Site																							
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 5%; text-align: center;">A</td> <td style="padding: 2px;">Reduced Freq, 2 to 3 yrs</td> </tr> <tr> <td style="text-align: center;">B</td> <td style="padding: 2px;">Moderate Freq, 1 to 2 Yrs</td> </tr> <tr> <td style="text-align: center;">C</td> <td style="padding: 2px;">increased Freq, &lt; 1 yrs</td> </tr> </table>	A	Reduced Freq, 2 to 3 yrs	B	Moderate Freq, 1 to 2 Yrs	C	increased Freq, < 1 yrs	<p>Using the Risk Rating,</p> <p>1) the estimated re-inspection date is (Please update in EudraGMDP): .....</p> <p>2) the delay of re-inspection based on Appendix 4 is: max.....(months/years)</p> <p>3) the date of the next inspection by the Supervisory Authority is (Please update in EudraGMDP): .....</p>																
A	Reduced Freq, 2 to 3 yrs																						
B	Moderate Freq, 1 to 2 Yrs																						
C	increased Freq, < 1 yrs																						

**Appendix 1 cont'd**

<b>PART F – Recommended Scope of the next Routine Inspection</b>	
<p>Note: This Part should be periodically updated if new information is received about the site before the next routine inspection that may warrant a change in risk rating and the scope of that inspection.</p> <p>For example, information can be received relating to, Quality Defects, Recalls, Market Surveillance Test Results, Enforcement Investigations, and other indicators of non-compliance, such as the failure to implement a variation to an MA that might require the scope of the next inspection to be changed. Information may also relate to major changes at the site (indicated perhaps via an MA variation or a manufacturing authorisation variation submission) and this may warrant a change in scope.</p>	
<p>Document on the right the <b>recommended focus &amp; depth</b> of the next routine inspection.  <b>Note:</b> Take into account the following:</p> <ul style="list-style-type: none"> <li>• The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies;</li> <li>• The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site;</li> <li>• The areas that were considered inadequately resourced at last inspection;</li> <li>• Planned changes at the site that may alter the complexity or criticality risk ratings associated with the site</li> <li>• Any other area that the inspector feels warrants review at the next inspection.</li> </ul>	
Document on the right the <b>required duration</b> of the next routine inspection:	
Document on the right the <b>required number of inspectors</b> that should be assigned to the next routine inspection:	
Document on the right any <b>specific competence or expertise</b> that will be required on the inspection team when performing the next routine inspection:	
<b>PART G – Signatures &amp; Dates</b>	
<p>Record here the names of the persons who completed this quality Risk management exercise, and sign and date this form:</p> <p>Name: _____ Name: _____</p> <p>Name: _____ Name: _____</p> <p style="text-align: center;">Signed: _____ Date: _____</p>	

## Appendix 2: Guidance on How to Score the Intrinsic Risk Factors

No.	Intrinsic Risk Factor & Scoring Mechanism
1	<p><b>Complexity</b></p> <p><b>This concerns the complexity of the site, its processes and its products.</b></p> <p>(Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Complexity score.)</p> <p>There are three possible scores here, 1, 2 and 3. Sites with a low risk factor score in this area are known to have a low level of complexity in the design of the site, in its products and processes. When scoring this Risk Factor, it is useful to consider the following:</p> <p>General but useful indicators of <b><u>site complexity</u></b> are:</p> <ul style="list-style-type: none"> <li>• The size of the site – large sites are rated more complex than smaller sites</li> <li>• The number of different manufacturing or distribution processes that are in use at the site – larger numbers generally give rise to more complexity</li> <li>• The level of dedication of equipment and facilities (e.g. Air Handling Units) that is in place at the site – sites with a low level of dedication are considered more complex than other sites</li> <li>• The number of staff at the site – larger numbers generally give rise to more complexity</li> <li>• The number of commercial markets/countries supplied by the site - larger numbers generally give rise to more complexity</li> <li>• The number of customers supplied by the site - larger numbers generally give rise to more complexity</li> <li>• If the site is a contract manufacturer or contract laboratory, the site can be regarded as being relatively complex</li> </ul> <p>General but useful indicators of <b><u>process complexity</u></b> are:</p> <ul style="list-style-type: none"> <li>• Sterile and aseptic manufacturing processes – these are always considered highly complex processes.</li> <li>• Parametric release activities – these are usually considered highly complex processes.</li> <li>• The number of critical steps that must be controlled within a process – generally, processes with a high number of critical steps can be considered to be more complex processes.</li> <li>• The type of products manufactured – some product types such as low-concentration/high potency dosage forms and sustained released dosage forms can be more complex to manufacture than other types of products (such as immediate release tablets) and the complexity of their manufacturing process should be rated more highly here.</li> <li>• The number of unit operations in a non-sterile manufacturing process - larger numbers generally gives rise to more complexity.</li> <li>• Repackaging activities - repackaging an already packaged batch can be considered a moderately to highly complex process.</li> <li>• The extent of reprocessing or reworking taking place at the site: these activities can add complexity to the process</li> <li>• Biological processes</li> </ul>

	<ul style="list-style-type: none"> <li>• The extent of subcontracting in use by the site - a significant use of contract manufacturers, off-site distribution sites or contract laboratories generally gives rise to complexity.</li> <li>• In case of importers, the complexity of importation, batch release and product distribution processes – sometimes the arrangements in place for importation can be quite complex.</li> </ul> <p>General but useful indicators of <b>product complexity</b> are:</p> <ul style="list-style-type: none"> <li>• The number of components that make up any one product pack - larger numbers of components in a pack generally give rise to more product complexity. For example, a pack of an injectable product may have 4 components within it (a lyophilised vial, a diluent vial, a transfer needle and a technical leaflet, whereas a pack of a tablet product may have just a blister strip and a patient information leaflet within it.)</li> <li>• Products requiring special storage and distribution: (e.g. cold chain products and short-shelf-life products such as radiopharmaceuticals can be complex to manage.)</li> </ul> <p><b>Tip: When considering product complexity, it is useful to imagine that you are holding a pack of the product in your hand and are asked: "What aspects of this product render it a complex product?"</b></p> <p>Scoring Guideline:</p> <p>Assign a score of 1 to sites with a low overall level of Complexity  Assign a score of 2 to sites with a moderate overall level of Complexity  Assign a score of 3 to sites with a high overall level of Complexity</p> <p>Note: When assigning the overall complexity rating, the rating (1, 2 or 3) which most reflects the various individual complexity ratings that were assigned to site, process and product complexity should be chosen. This is similar to taking an average of all of the individual complexity ratings that were assigned.</p> <p>In cases where there is insufficient information or knowledge about the complexity associated with the site, its processes and products, a medium score of 2 should be assigned.</p>
2	<p><b>Criticality:</b></p> <p><b>This concerns how critical the availability of the products manufactured by the site is from a supply perspective, or how critical the services provided by the site are. An example of a critical service provided by a site may be an analytical testing service performed for several other companies.</b></p> <p>(Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Criticality score.)</p> <p>There are three possible scores here, 1, 2 and 3.</p> <p>Scoring Guideline:</p> <p>Assign a high score (of 3) to sites that are known to manufacture essential products or that are known to be sites that provide an essential service that is not readily available elsewhere.</p>

Figure: 1. These may be sites that are the major or sole supplier of an essential product (such as an important vaccine, a critical blood product, etc.). Note: it is recognised that being the major or the sole supplier of an essential product does not present any risk to product quality; rather, it presents a risk to product availability.

Figure: 2. The test methods (and related equipment) used by these sites cannot easily or readily be performed or used by other laboratories.

Figure: 3. These may be sites that provide a contract manufacturing or testing service to a number of other manufacturers and a disruption in such services would have a significant impact on product availability.

Figure: 4. Assign a low score (of 1) to sites that are known to manufacture only non-essential products or that are known to be sites that do not provide an essential service.

Figure: 5. These may be sites that are not the sole supplier of any important products (such as an important vaccine, a critical blood product, etc.).

Figure: 6. The test methods (and related equipment) used by these sites are not such that they cannot be readily performed or used by other laboratories.

Figure: 7. These are not sites that provide a contract manufacturing or testing service to many other manufacturers, where a disruption in such services would have a significant impact on product availability.

Assign a medium score (of 2) to sites that are in between the above types of sites.

Note: In cases where there is insufficient information or knowledge about the criticality associated with the site, a medium score of 2 should be assigned.



### Appendix 3- Expenditure of Time

Classification of manufacturing or importation sites according to the type of product/process		Overall inspection days
<b>1.1</b>	<b>Sterile Products</b>	
	<b>1.1.1 Aseptically prepared (list of dosage forms)</b> 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	<b>≥ 10</b>
	<b>1.1.2 Terminally sterilised (list of dosage forms)</b> 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	<b>≥ 8</b>
	<b>1.1.3 Batch certification only</b>	<b>≥ 1</b>
<b>1.2</b>	<b>Non-sterile products</b>	
	<b>1.2.1 Non-sterile products (list of dosage forms)</b> 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	<b>≥ 4</b>
	<b>1.2.2 Batch certification only</b>	<b>≥ 1</b>
<b>1.3</b>	<b>Biological medicinal products</b>	
	<b>1.3.1 Biological medicinal products</b> 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	<b>≥ 7</b>
	<b>1.3.2 Batch certification only (list of product types)</b> 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	<b>≥ 1</b>

<b>1.4</b>	<b>Other products or manufacturing activity</b>	
	<p><i>1.4.1 Manufacture of:</i></p> <p>1.4.1.1 Herbal products 1.4.1.2 Homoeopathic products 1.4.1.3 Biological active starting materials</p> <p><i>1.4.2 Sterilisation of active substances/excipients/finished product:</i></p> <p>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</p>	<p><b><u>&gt; 3</u></b></p> <p><b><u>&gt; 2</u></b></p>
<b>1.5</b>	<b>Packaging only</b>	
	<p><i>1.5.1 Primary packing</i></p> <p>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</p>	<b><u>&gt; 2</u></b>
	<i>1.5.2 Secondary packing</i>	<b><u>&gt; 1</u></b>
<b>1.6</b>	<b>Quality control testing</b>	
	<p><i>1.6.1 Microbiological: sterility</i> <i>1.6.2 Microbiological: non-sterility</i> <i>1.6.3 Chemical/Physical</i> <i>1.6.4 Biological</i></p>	<b><u>&gt; 2</u></b>

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 equal 2 inspectors inspecting for 5 days or 4 inspectors inspecting for 2½ days; preparation and report time included).

**Appendix 4: Guidance on the delay of a re-inspection based on compliance information from a trusted authority**

**Procedure Steps:**

**1a. Select sites based on the compliance risk** resulting from the last inspection by the Supervisory Authority (in line with Appendix 1 Part C, and item 5.1.3. of the procedure).

**1b. Determine the intrinsic risk of the site** (in line with Appendix 1 Part B and item 5.1.2. of the procedure).

**2. Request compliance information** from a trusted authority that has inspected the site since the last inspection by the Supervisory Authority.

**3. Evaluate the compliance information received from the trusted authority** to establish the Current Compliance Risk (in analogy to Step 1a and Item 5.3.1 of the procedure whereby deficiencies reported by the trusted authority may have to be re-categorised in line with the EU definitions of “critical” and “major”.)

**4. Delay the routine re-inspection** by the Supervisory Authority in line with the below table and document this in Appendix 1 Part E.

	Step 1a	Step 1b		Step 2	Step 3	Step 4
Scenario	Compliance Risk post last inspection	Intrinsic Risk	Risk Rating	Request compliance information from a trusted authority.	Current Compliance Risk	Re-Inspection Delay (+ max. years)
Trusted Authority's domestic site but product NOT in the operational scope of a legal agreement	Low	High	B		Low	+1
	Low/Medium	Medium	A/B		Medium	+1
	Low/Medium	Medium	A		Low	+1.5
	Low/Medium	Low			Medium	+1.5
	Low/Medium	Low			Low	+2
THIRD COUNTRY <sup>1</sup> site but product in the operational scope of a legal agreement	Low/Medium	Medium	A/B		Medium	+1
	Low/Medium	Medium	A		Low	+1.5
	Low/Medium	Low			Medium	+1.5
	Low/Medium	Low			Low	+2
THIRD COUNTRY site and product NOT in the operational scope of an agreement or no legal agreement in place	Low/Medium	Low	A	Medium	+1	
	Low/Medium	Low		Low	+1.5	

<sup>1</sup> Third Country = outside of the EU/EEA

# Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health

## Table of contents:

1. Principles
2. Definitions
3. Scope
4. Procedure for issuing a GMP non-compliance statement
5. Notification to the European medicines regulatory network
6. Disagreement
7. Appendices

<b>Title</b>	<b>Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health

## 1. Principles

All GMP inspections carried out by the inspection services of any Member States are performed on behalf of the entire European Union. 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.

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. Authorities should endeavour to evaluate the consequences for public or animal health and agree in as far as practicable on common actions in advance of the issuance of the statement of non-compliance. Therefore a mechanism that ensures consistent, co-ordinated measures for protection of public and/or animal health are taken throughout the Union is required. 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 action to protect public or animal health to be taken without delay.

Where an inspection of an active substance manufacturer has been carried out at the request of the European Directorate for the Quality of Medicines and HealthCare (EDQM) in connection with the "Certification of Suitability to the monographs of the European Pharmacopoeia" inspectorates have a dual responsibility to follow this procedure for notifying national competent authorities of the serious GMP non-compliance and to follow the procedures established by EDQM to determine the consequences for the certification(s) in question. Inspectorates should ensure that a co-ordinated approach is followed.

Suspension or withdrawal of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) may be a recommended action following an inspection of an active substance manufacturer and so 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.

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. This procedure requires the inspectorate discovering serious GMP non-compliance to recommend appropriate action following a supervisory risk assessment, involving other authorities that share supervisory responsibility in developing those recommendations, and to communicate the recommendations to all other authorities in the Union. Communication with authorities of those countries, with which the Union has made appropriate arrangements on GMP (e.g. mutual recognition agreement (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.

National competent authorities (NCAs) must take into account the information on serious GMP non-compliance received and should provide information requested and 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.

The reporting inspectorate should enter the information on serious GMP non-compliance in EudraGMDP, as referred to in Article 111(6) of Directive 2001/83/EC (as amended) and Article 94 (2) of Regulation 2019/6 (as amended). In the case of a serious GMP non-compliance of an active substance manufacturer and where the inspection is in the context of the CEP, every effort should be made to align the entry of the final non-compliance statement into EudraGMDP with the final publication by EDQM of any supervisory action concerning affected CEPs.

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

With regard to supervisory actions, directly or consequential, against marketing authorisations, the Reference Member State (RMS) takes the initiative for mutual recognition/de-centralised products. Where more than one RMS is involved, a co-ordinated approach should be followed according to the "Best practice guidance on collaboration between Member States in relation to GMP non-compliance issues" of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) is involved in the case of veterinary medicinal products although no best practice guidance exists.

The European Medicines Agency takes the initiative and co-ordinates action for centrally authorised products (CAPs). Member States should ensure that their CMDh/CMDv or Committee for Medicinal Products for Human Use (CHMP)/Committee for Medicinal Products for Veterinary Use (CVMP) representative(s) as appropriate are involved in relevant discussion at national level during the evaluation phase and when implementing actions. Each national competent authority takes responsibility for marketing authorisations that exist purely at national level, but may wish to bring the discussion forward for collaborated evaluation at the level of CMDh or CMDv, according to the above mentioned CMDh procedure or CMDv.

GMP non-compliance may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. It may be necessary to elevate the assessment to a union level in order to protect public or animal health.

The objective of the procedure should be to achieve a co-ordinated and harmonised (where possible) assessment and supervisory actions to ensure maximum efficiency and avoid full parallel reviews on a national level across the EEA.

It is understood that a manufacturer 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 action to protect public or animal health being taken.

## **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 urgent interim supervisory measures may be necessary to remove a potential risk to public or animal health or where final measures may be needed to prohibit further supply of the medicinal product. Serious

GMP non-compliance may include deficiencies as a result of evidence of falsification gathered by inspectors during GMP inspection.

- 2.2** For the purposes of this procedure, urgent measures may include but are not limited to prohibition of manufacture or importation, supply or withdrawal of medicinal products, where the action may be limited to specific batches or suspension of an existing manufacturer or import authorisation.
- 2.3** For the purpose of this procedure final measures may include but are not limited to actions taken by an authority to revoke, or vary an existing marketing authorisation/manufacturer or import authorisation or refuse an application for marketing authorisation /manufacturer or import authorisation.

### **3. Scope**

- 3.1** 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 supervisory action being taken. This procedure applies only when the level of non-compliance is such that the inspector concerned recommends that supervisory 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. Procedure for issuing a GMP non-compliance statement**

This procedure should be followed, and if action to protect public or animal health is indicated this should be communicated to other competent authorities in accordance with this procedure, within a timeframe appropriate to the potential threat to public or animal health.

It may be necessary to issue the non-compliance statement without complete information if the risk to patient health is considered particularly severe.

### **4.1 Finalisation of inspection report and conclusion on GMP compliance**

#### **4.1.1 Finalise the summary of inspection findings: critical and major GMP deficiencies**

##### **Responsibility: inspection team**

Following a GMP inspection leading to a conclusion of GMP non-compliance, the inspection team should have made their concerns clear to the inspected site. It may not be possible to finalise the inspection report in time to take the appropriate measures to protect public or animal health and therefore the inspection team should draft a summary of inspection findings describing the critical and major GMP deficiencies.

The inspection report may be prepared and finalised separately and should be available to competent authorities on request. The finalised report must conclude whether the inspected company complies with the principles and guidelines of GMP or not.

#### **4.1.2 Review the summary of the critical and major findings**

##### **Responsibility: lead inspectorate authority**

Each national competent authority should have an internal procedure to review inspection reports, (draft) non-compliance statements and supervisory risk assessments (refer to 4.2.3) prepared by 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 internal procedure should take into account the need for co-operation and collaboration with other departments within the respective authority (e.g. market surveillance or pharmaceutical or clinical assessment) and with international partners where appropriate and with enforcement officers or national enforcement authority in the case of non-compliance due to falsification.

#### **4.1.3 Finalise recommendations following assessment**

##### **Responsibility: lead inspectorate authority**

Any recommendations made by the authority reporting the serious GMP non-compliance must take account of the interests of the Union as a whole, regardless as to any specific national considerations.

#### **4.2 Pre-issuance of statement of non-compliance and supervisory risk assessment**

##### **Responsibility: lead inspectorate authority**

If the inspection report concludes that the inspected company does not comply with GMP, then the lead inspectorate authority concerned should prepare a draft non-compliance statement and a supervisory risk assessment, discussing the impact of the inspection findings on medicinal products that are known to be on the market or in use in clinical trials or under evaluation at that time (and may be amended pending receipt of further information).

##### **4.2.1 Gather information on the medicinal products manufactured at the site**

##### **Responsibility: lead inspectorate authority**

In so far as is possible, the lead inspectorate authority that carried out the inspection revealing the non-compliance should establish the following as appropriate:

- (a) The identity of Member States with products directly affected by the inspection findings.
- (b) The marketing authorisations involved and where relevant, the RMS(s) and the competent authority(ies) responsible for the marketing authorisation(s).
- (c) The identity of other supervisory authorities in the case of medicinal or investigational medicinal products or active substances imported into the Union.
- (d) For investigational medicinal products the EudraCT trial reference numbers should be identified.

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 lead inspectorate authority.

The lead inspectorate authority that carried out the inspection should involve the sponsor as well as the manufacturer or importer in order to identify all affected trials.



- (e) In the case of inspections of active substance manufacturers, all the active substances manufactured at the site and/or any CEPs that may be affected.

#### **4.2.2 Prepare a draft statement of non-compliance**

##### **Responsibility: lead inspectorate authority**

The issuing authority should prepare a draft statement of non-compliance using the agreed Union format.

The draft statement of non-compliance should explain the nature of any proposed action, or where justified, action already taken.

#### **4.2.3 Prepare the supervisory risk assessment**

##### **Responsibility: lead inspectorate authority**

The inspecting authority's supervisory risk assessment should be appended to the draft statement of non-compliance.

The supervisory risk assessment should evaluate the critical and major GMP deficiencies and the overall risk to product quality and product supply and recommend what risk-mitigating action is appropriate. This could include i) a recall for products/batches released onto the market, ii) a prohibition of importation and/or supply and/or iii) administrative action with respect to the manufacturing or marketing authorisation or CEP, if appropriate.

The supervisory risk assessment should have the following structure:

- (a) Introduction / background;
- (b) Main inspection findings recorded which may lead to issuance of statement of non-compliance with GMP;
- (c) Assessment of main inspection findings on concerned medicinal products, and whether these risks should be applied retrospectively from the date of the statement of non-compliance or earlier;
- (d) NCA recommendations for interim urgent measures and final supervisory actions commensurate with identified risks. Any recommendations with respect to the marketing authorisation should be strongly motivated and commensurate with the level of risk;
- (e) If an inspection of an active substance manufacturer has been carried out, the impact or otherwise on any other active substance manufactured at the same site and any CEP should be considered;
- (f) Implications for product supply based on information available to the inspectorate.

A template for the preparation of the supervisory risk assessment is provided in Appendix 6.

#### **4.2.4 Circulate draft statement of non-compliance & supervisory risk assessment**

##### **Responsibility: lead inspectorate authority**

In principle unilateral action by one member state should be avoided, unless justified. In order to facilitate co-ordinated action at Union level, the draft statement of non-compliance should be circulated prior to the execution of any action.

The draft statement of non-compliance and supervisory risk assessment should be distributed to EEA Member States via the rapid alert distribution list. 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 draft statement of non-compliance.

The lead inspectorate may request additional information from competent authorities and the timeframe indicated should take into account the level of risk and the amount of information to be gathered. National competent authorities should reply to the lead inspectorate by the timeframe indicated even if no impact is anticipated.

#### **4.2.5 Receipt and evaluation of the (draft) statement of non-compliance and supervisory risk assessments**

##### **Responsibility: national competent authorities**

On receipt of the draft statement of non-compliance, authorities should check whether nationally authorised products on their own territories are affected, and whether they are the RMS for any affected products, seeking assistance from the inspectorate carrying out the inspection, if different, as needed.

Member states and regulatory partner agencies who are in receipt of the draft statement of non-compliance and supervisory risk assessment must treat the documents and information contained therein as confidential. At this stage in the process it is unlikely that final regulatory or market place actions will have been agreed, and circulation of information outside the regulatory network risks a loss of coordinated action, with resultant risks to public and/or animal health. Communication with the manufacturing site should be coordinated via the lead inspectorate authority, and wherever possible communication with affected marketing authorisation holders or importers regarding compliance issues should be deferred until a consensus on coordinated action has been agreed across the Union.

Each national competent authority should have a procedure to review and, assess (draft) non-compliance statements and supervisory risk assessments transmitted through the rapid alert system. This procedure should take into account the need for co-operation and collaboration with other departments within the respective authority (e.g. product licencing, market surveillance or clinical or pharmaceutical assessment), and with the national licensing authority (where different) and with international partners where appropriate and with enforcement officers or national enforcement authority in the case of non-compliance due to falsification.

The procedure should ensure that information requested by an inspectorate can be obtained and returned within the timeframe indicated.

In cases where a non-compliance report will impact on a CEP, EDQM will evaluate the supervisory risk assessment and will decide on the action to be taken following their decision making procedure.

#### **4.3 The teleconference**

A rationale should be provided in the notification form if no teleconference is proposed.

Points to consider for authorities on when to hold a teleconference and practical arrangements in hosting the teleconference are appended to this procedure (Appendix 2).

#### **4.3.1 Organising the teleconference**

##### **Responsibility: lead inspectorate authority**

Where relevant, a contact telephone number should be given in the draft GMP non-compliance 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.

The EDQM should be invited to join the teleconference if the non-compliance relates to an active substance manufacturer named on a CEP.

#### **4.3.2 Joining the teleconference**

##### **Responsibility: national competent authorities**

If a member state is affected, or if a Member State is RMS for a product that is affected, 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. If the proposed actions include variations to Marketing Authorisation(s) the RMS(s) should take the lead in implementing such actions.

The objective of the teleconference should be to co-ordinate and harmonise where possible the assessment and actions to ensure maximum efficiency and avoid full parallel reviews on a national level across the EEA.

#### **4.3.3 Communicating the outcome of the teleconference**

##### **Responsibility: lead inspectorate authority**

The outcome of the teleconference, if held, should be communicated in a follow up message to the network via rapid alert contact points to confirm that the recommended action in the initial notification was agreed or to communicate any other agreed Union action.

#### **4.4 Urgent measures to protect public and animal health**

On receipt of the draft non-compliance statement, receiving authorities should verify the implications for public and animal health and adapt national actions as necessary.

##### **4.4.1 Evaluating the impact of the GMP non-compliance statement on the quality and safety of batches on the market or awaiting release**

##### **Responsibility: lead inspectorate authority**

The lead inspectorate authority reporting the serious GMP non-compliance should recommend if urgent interim measures to safeguard public and/or animal health by removing batches from commercial circulation or in use in clinical trials and/or to prohibit further distribution and/or importation of concerned batches is necessary. The lead inspectorate authority should evaluate, where possible, the impact of the GMP non-compliance statement on the quality and safety of batches on the market or awaiting release. In cases where such evaluation is not possible due to insufficient information, the lead inspectorate should provide support to this evaluation process by supplying details regarding the deficiencies observed and the potential global impact of the products.

Recommendation on recall or prohibition of supply should be discussed with the relevant authorities at the teleconference. As far as practicable a harmonised Union action plan and

timetable should be achieved and agreed. It is recognised that in some cases different actions may be necessary in different Member States due to the criticality of the medicinal products concerned. Criticality of medicinal products should be assessed following agreed criteria (Appendix 3). Differences in approach should be recorded in the minutes of the teleconference.

In the event that supply shortages will be caused at a Union level, as a result of proposed measures to be taken due to non-compliance with GMP, consideration should be given to initiating the procedure described in "The European Union regulatory network incident management plan for medicines for human use" or the corresponding procedure for veterinary products. In the case of medicinal products for human use, further guidance on when it is necessary to elevate the discussion to Union level in order to agree on a harmonised risk management strategy in order to protect public health is available (Appendix 4).

#### **4.4.2 Deciding to issue a rapid alert**

##### **Responsibility: lead inspectorate authority**

If it is considered necessary to remove products or certain batches from the market, the lead inspectorate authority is responsible for issuing the rapid alert. If there is a differential approach to product recall in Member States, agreement should be reached on responsibility for transmission of the initial rapid alert.

Recalls and rapid alerts should be classified and transmitted in accordance with Union procedures.

#### **4.4.3 Deciding to prohibit supply**

##### **Responsibility: supervisory authority / competent authority**

It may be necessary to urgently prohibit importation and supply through an appropriate supervisory measure.

#### **4.5 Publication of statement of non-compliance**

##### **4.5.1 Finalisation and entry into EudraGMDP**

##### **Responsibility: lead inspectorate authority**

The lead inspectorate should then finalise the statement of non-compliance and/or restricted GMP certificate (see 4.5.3) and enter into EudraGMDP.

##### **4.5.2 Impact on other EudraGMDP entries for the manufacturing site**

##### **Responsibility: lead inspectorate authority**

Existing valid GMP certificates with conflicting information will be superseded and should therefore be withdrawn in accordance with the Union procedure for the issue and update of GMP certificates.

##### **4.5.3 Entry of restricted GMP certificate into EudraGMDP**

##### **Responsibility: lead inspectorate authority**

If, following discussion at the teleconference, a risk-based decision is agreed to allow further release and distribution of batches of critical product(s) from the site concerned, an

appropriately restricted GMP certificate may be issued as well as a statement of non-compliance.

In other 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.

#### **4.5.4 Notification of relevant authorities where the manufacturer is located**

##### **Responsibility: lead inspectorate authority**

Where the GMP non-compliance is discovered at a third country manufacturing site the inspectorate concerned should notify the relevant authorities of the third country of the issuance of the statement of non-compliance. The inspectorate should seek co-operation from the concerned third country authority in overseeing correction at the manufacturing facility.

In the case of third country manufacturers of active substances, the concerned third country authority should be notified of the issuance of the statement of non-compliance using the template provided in Appendix 5. The third country authority should be asked to withdraw any previously issued written confirmations of API compliance, and to notify the supervisory EU authority when compliance equivalent to EU GMP is considered to have been restored by the manufacturer. As the statement of non-compliance takes precedence over a written confirmation, resumption of supply to the EU may take place only following a satisfactory re-inspection by an EU authority, or MRA partner agency (if recognition of inspections in third countries is covered by the MRA).

#### **4.5.5 Notification of MRA partners**

##### **Responsibility: lead inspectorate authority**

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. This is done automatically by EudraGMDP.

#### **4.5.6 Notification of third countries**

##### **Responsibility: lead inspectorate authority**

Third countries with which the Union has concluded an arrangement and which have been given access to EudraGMDP will be notified automatically of statements of non-compliance placed into the database.

In the case of a non-compliance statement issued following an inspection of a manufacturer of active pharmaceutical ingredients located in the EU, the lead inspectorate should notify the authority of any third country that is supplied by that manufacturer. Notification may consist of a statement that a non-compliance statement has been uploaded to EudraGMDP.

#### **4.5.7 Post-publication modifications**

##### **Responsibility: lead inspectorate authority**

Following the publication, the lead inspectorate authority may have to modify the non-compliance information entered in EudraGMDP for example, following receipt of new information. The modified statement of non-compliance should be distributed to the rapid alert distribution list drawing attention to those sections that have been altered.

### **4.6 Non-Urgent Measures to protect public and animal health**

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On receipt of the final non-compliance statement, receiving authorities should verify the implications for public and animal health and adapt national actions as necessary.

#### **4.6.1 Evaluating and deciding the impact of the statement of non-compliance on marketing authorisations (applications)**

##### **Responsibility: EMA or RMSs (including consultation with CMSs and discussion at CMDh/CMDv if necessary)**

The evaluation of the impact of the statement of non-compliance on marketing authorisations (applications) should take into account the appropriate legal framework for granting the marketing authorisation as well as the potential impact of the findings on any data submitted to the competent authority. Any decision to suspend a marketing authorisation has to be strongly motivated and the principle of proportionality taken into account.

In the case of evaluation of the impact on marketing authorisations (applications) subject to the de-centralised/mutual recognition procedures, the RMS should take the initiative in following the recommendations of the authority reporting the non-compliance.

In the case of actions proposed for marketing authorisations (applications) subject to the de-centralised or mutual recognition procedures, CMDh or CMDv may decide to discuss the coordination of actions at a meeting of the relevant group before implementation.

In the case of action against centralised marketing authorisations (applications), the European Medicines Agency will co-ordinate evaluation via the CHMP and/or CVMP.

Each national competent authority takes responsibility for marketing authorisations (applications) that exist purely at national level, but collaboration at EU level may be sought by tabling the issue for further discussion at CMDh/CMDv.

The appropriate competent authorities should decide whether a marketing authorisation should be suspended, revoked or varied and/or whether a marketing authorisation application should be refused as a result of the non-compliance with GMP.

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. It may be possible to protect public health through the removal of a noncompliant site through variation of the marketing authorisation.

Member States should inform EMA as appropriate following the procedure in Article 123 of Directive 2001/83/EC (as amended) for human medicinal products. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the procedure set out in article 123 of Directive 2001/83/EC for human medicinal products.

#### **4.6.2 Evaluating and deciding on the impact of the GMP non-compliance statement on clinical trials**

##### **Responsibility: national competent authorities**

Where action may have an impact on clinical trials, national competent authorities should involve the Clinical Trial Facilitation Group (CTFG).

Each national competent authority authorising the trial in question should evaluate the impact of the GMP non-compliance statement on the quality and safety of the investigational medicinal product and in some cases the results of completed trials may need to be re-evaluated.

Each national competent authority authorising the trial in question should decide on the appropriate measure to be taken.

Where the agreed action is suspension or termination of a clinical trial each national competent authority having authorised the trial in question should make an appropriate entry into the EU clinical trial database.

#### **4.6.3 Evaluating and deciding on the impact of the GMP non-compliance statement on CEPs**

##### **Responsibility: EDQM**

If an inspection of an active substance manufacturer has been carried out at the request of EDQM and serious non-compliance is found, the EDQM is responsible for evaluating and deciding on the impact of the non-compliance statement on the CEP(s).

The lead inspectorate and EDQM should ensure that issuance of the final statement of non-compliance with GMP should be aligned with the issuance of the final decision of EDQM's ad-hoc committee on the validity of CEP(s).

#### **4.6.4 Evaluating and deciding on the impact of the GMP non-compliance statement on manufacturing / import authorisation(s)**

##### **Responsibility: supervisory authority**

Supervisory authorities should evaluate whether a manufacturing or import authorisation should be suspended (total or partial), varied or revoked as a result of the non-compliance with GMP. Similarly, an application for a manufacturing or import authorisation may be suspended or refused.

The Supervisory Authority should decide whether a manufacturing or import authorisation should be, suspended (total or partial), varied or revoked as a result of the non-compliance with GMP.

The supervisory authority should decide on the consequential entry required in the EudraGMDP database.

GMP non-compliance found at an active substance manufacturer may indicate 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.

#### **4.6.5 Evaluating and deciding on the impact of the suspension or withdrawal of the CEP on the marketing authorisation (application)**

##### **Responsibility: RMSs (including consultation with CMSs and discussion at CMDh/CMDv if necessary) EMA / or NCA's**

If a CEP is suspended or withdrawn the appropriate competent authorities should assess the reasons for the suspension or withdrawal and decide whether a marketing authorisation should

be suspended, revoked, or varied and/or whether a marketing authorisation application should be refused as a result of the consequent suspension or withdrawal of the CEP due to the non-compliance statement.

The appropriate competent authorities should consider requesting that alternative active substance manufacturer 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.

## **5. Suspension or withdrawal of CEPs for non-GMP reasons**

CEPs may be suspended or voided for reasons unrelated to inspections, for example failure to fulfil critical commitments.

### **5.1 Notification to the European medicines regulatory network**

#### **Responsibility: EDQM**

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 clearly indicate the reasons for suspension or withdrawal.

#### **5.1.1 Evaluating the impact of the suspension or withdrawal of the CEP on quality and safety of batches on the market**

##### **Responsibility: RMS (including consultation with CMSs and discussion at CMDh/CMDv if necessary) / EMA / NCA**

Reasons for CEP withdrawal or suspension other than noncompliance with GMP may include but are not limited to for example, the inability to manufacture in accordance with the current monograph (i.e. when a revised monograph has been introduced), impact of local regulatory restrictions placed on the manufacturer (e.g. environmental) or temporary interruption of manufacturer at the request of the CEP holder based on commercial reasons.

In the event that a recall is necessary in response to CEP withdrawal or suspension for reasons other than noncompliance with GMP, responsibility for issuing the rapid alert is as follows:

Figure: 1. For affected products subject to the decentralised or mutual recognition procedures the Reference Member State,

Figure: 2. For centrally authorised products, the European Medicines Agency will coordinate in the same way as a quality defect.

Figure: 3. For products subject to national marketing authorisations only, a national recall may suffice.

#### **5.1.2 Evaluating and deciding on the impact of the suspension or withdrawal of the CEP on the marketing authorisation (application)**

##### **Responsibility: RMS (including consultation with CMSs and discussion at CMDh/CMDv if necessary) / EMA / NCA**



Following 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 RMS.

The European Medicines Agency through the scientific committees, will assess any impact on centrally authorised products and co-ordinate any associated supervisory action.

The RMS should take the initiative in proposing an action on marketing authorisations subject to the mutual recognition or de-centralised procedures and consulting with the CMSs and the decision is taken nationally. The appropriate competent authorities should assess the reasons for the suspension or withdrawal and decide whether a marketing authorisation should be suspended, revoked, or varied and/or whether a marketing authorisation application should be refused as a result of the consequent suspension or withdrawal of the CEP.

The appropriate competent authorities should consider requesting that alternative active substance manufacturer be added through a variation unless an alternative active substance manufacturer is already authorised, in which case the active substance manufacturer named on the CEP in question should be removed through a variation.

Individual national competent authorities should take action against the marketing authorisation in the case of products authorised solely on a national basis.

## **6. Disagreements**

### **6.1 Disagreeing with the outcome of the inspection**

#### **Responsibility: national competent authorities**

Disagreement with the outcome of the inspection should be dealt with through procedures established in accordance with Art. 122 of Directive 2001/83/EC (as amended) for human products. In such cases Art. 122(3) of Directive 2001/83/EC obliges the Member State in question to notify the European Medicines Agency and the Commission. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the same arbitration procedure set out in article 122 of Directive 2001/83/EC for human medicinal products.

### **6.2 Disagreeing with the outcome of the assessment of the impact of the non-compliance statement**

#### **Responsibility: national competent authorities**

Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Union 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.

## **7. Appendices**

### Appendix 1: Flowchart

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Appendix 2: Points to consider when a teleconference is convened by the lead inspectorate authority

Appendix 3: Criteria for classification of critical medicinal products, EMA/314762/2013

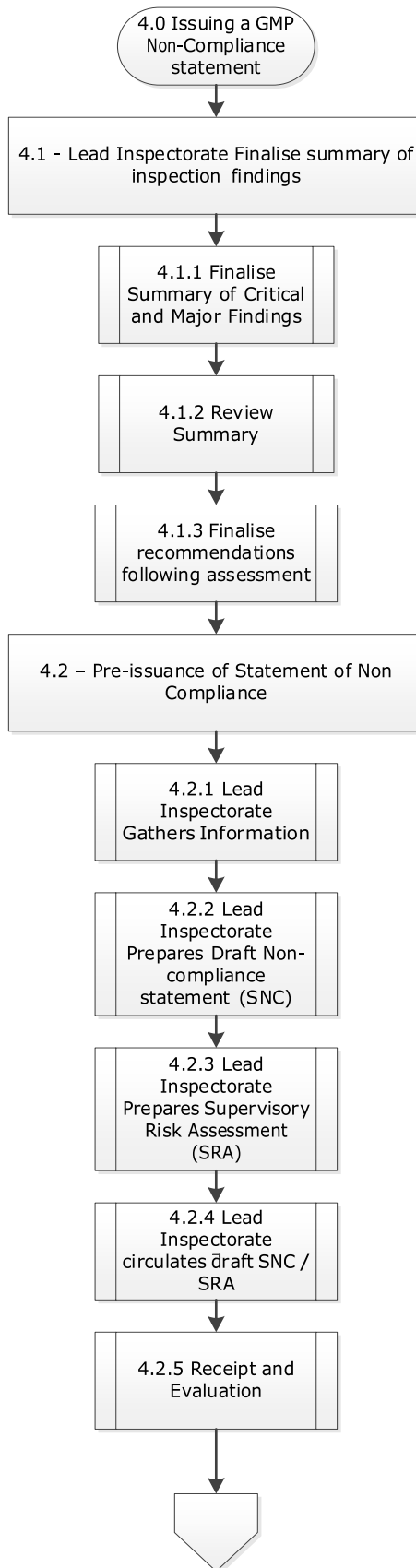
Appendix 4: Decision tree on escalation from national to European level, EMA/314722/2013

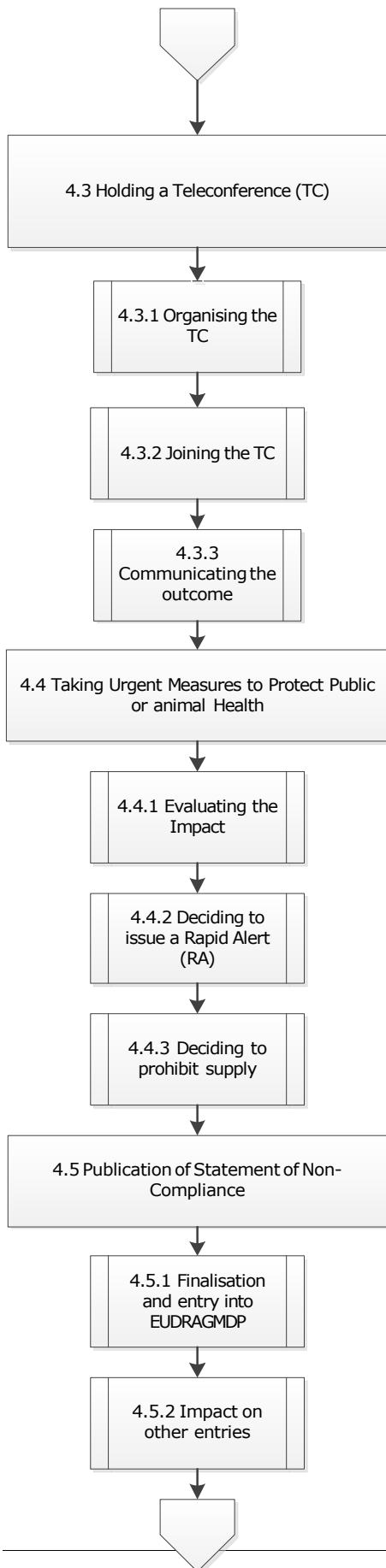
Appendix 5: Template to 3<sup>rd</sup> country authorities issuing written confirmations

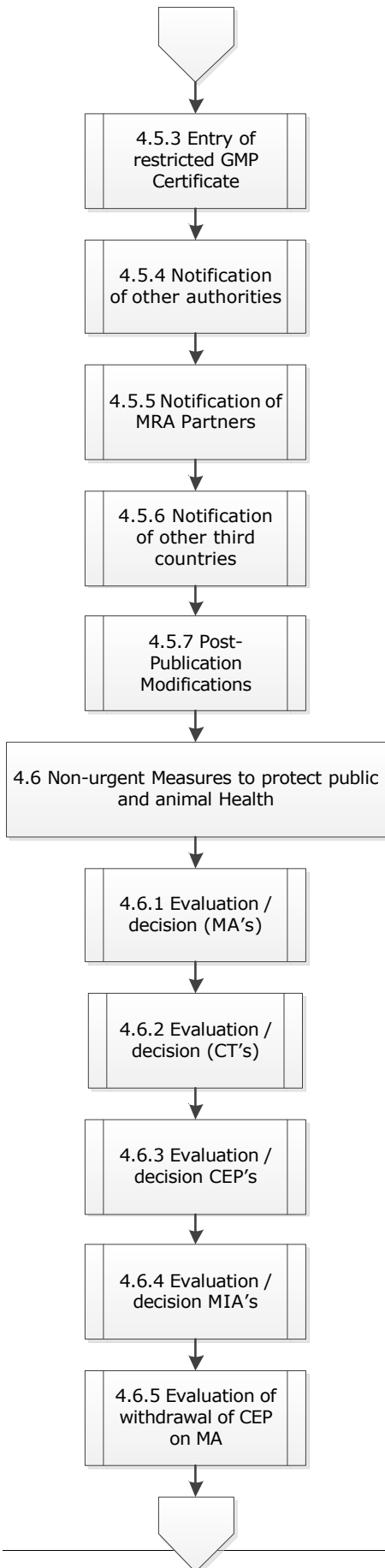
Appendix 6: Supervisory Risk Assessment

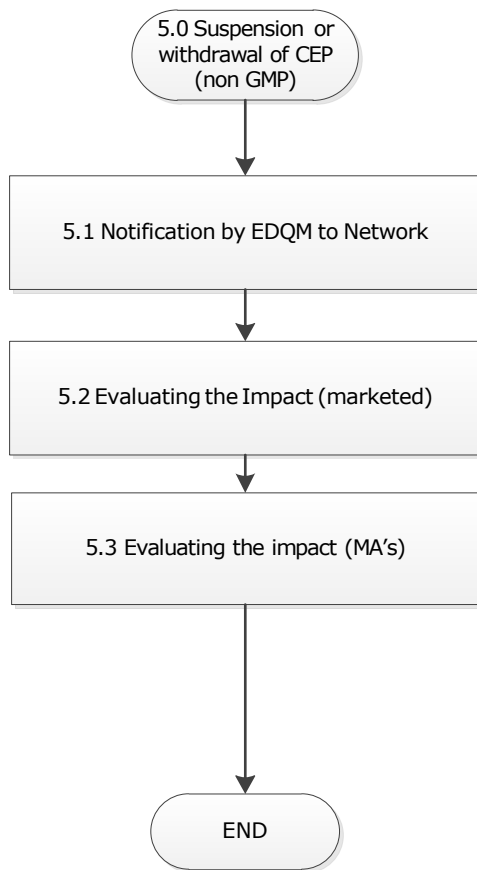
# Appendix 1:

## Annex 1









## **Appendix 2: Points to consider when a teleconference is convened by the lead inspectorate authority**

### **1. Introduction**

The Union procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action requires that the lead inspectorate authority should organise 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 Union level.

The purpose of this document is to outline the main points for consideration for the issuing authorities and for the receiving authorities who are participating in the teleconference.

#### **1.1 When to organise a teleconference**

A teleconference may be indicated if the manufacturer or importer of the medicinal product is supplying more than one EEA member state and;

Figure: 1. The supervisory risk assessment indicates that urgent interim measures such as a product recall will be necessary.

Figure: 2. The supervisory risk assessment indicates that prohibition of importation or further supply of the concerned medicinal product(s) will be necessary.

Figure: 3. The supervisory risk assessment indicates that measures will have to be taken against the manufacturing/importation or marketing authorisation(s).

Similar considerations apply if the non-compliance concerns a manufacturer of the active pharmaceutical ingredient.

#### **1.2 Practical considerations**

The lead inspectorate authority should take the lead in organising and chairing the teleconference. In the case where centrally authorised products are involved, the lead inspectorate authority may agree that EMA organise the TC.

The issuing authority should circulate a draft agenda and participant list in advance of the TC. Each concerned authority should ensure that all meeting participants are identified to the lead inspectorate authority.

The chairman should clearly state and agree with the participating authorities the purpose and objectives of the TC and should clearly summarise the main decisions taken by the participants.

The lead inspectorate authority is responsible for ensuring that minutes/table of actions of the teleconference are taken and agreed with participants. The distribution of the final minutes/table of actions to Member States should be within two weeks of the date of the teleconference.

## **Appendix 3 - Criteria for classification of critical medicinal products**

### **Shortages due to GMP non-compliance/quality defects**

#### **1. Introduction**

GMP non-compliance/quality defects may lead to shortage of a product, if it is decided not to release a batch or even to withdraw batches from the market. Though in general such action based on GMP issues/quality defects is good precautionary practice, there might be situations where withdrawing a product or not releasing it might do more harm to a patient than allowing a product to remain on the market.

The classification of a medicinal product as critical should be performed by CHMP for centrally authorized products (CAPs) or by Member States for non-CAPs taking into account the criteria expressed in this document and supply situations at a national level.

At the moment there is no harmonized approach to such classification, as situations might be different in different countries. Products and/or alternatives may or may not be available and use of products may depend on national preferences. In the following a proposal is made for a more harmonized way of handling the classification of a medicinal product as 'critical'.

The principles set out in this paper may also apply when shortages due to other reasons are encountered, at the Member States' discretion.

#### **2. Criteria for classification**

When defining a product as critical, two criteria are of importance: therapeutic use and availability of alternatives.

##### **A. Therapeutic use**

The medicinal product is an integral part of the treatment for a disease, which is life-threatening or irreversibly progressive, or without which the patient could be severely harmed.

This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where the product has been shown to affect the progression of the disease or survival.

##### **B. Availability of alternatives**

Even if the product would be used in the situation defined above, it would not be classified as being critical in case appropriate alternatives are available. These could be:

- Alternative manufacturing site for the same product; caveat: manufacturing capacity and technical and regulatory times to switch.
- Different strength/formulations of the same product; caveat: need for formulations suitable for use in special populations.



- Alternative dosing (lower dose/temporary break from drug treatment) or limiting the use to high risk patients could be explored; caveat: this might depend on the expected duration.

## **Appendix 4 – Decision tree on escalation from national to European level**

### **Shortages due to GMP non-compliance/quality defects**

#### **1. Introduction**

GMP non-compliance/quality defects may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. Though in general such action based on GMP non-compliance/quality defects is good precautionary practice and at the discretion of the Member States when products are authorized nationally, there might be incidents where it is necessary to elevate the discussion to agree on a harmonized risk management strategy at a Union level in order to protect public health.

The principles set out in this paper may also apply when shortages due to other reasons are encountered, at the Member States' discretion.

#### **2. Problem statement**

Supply incidents caused by GMP non-compliance/quality defects may be managed and controlled with the aid of the EU regulatory network incident management plan for medicines for human use.

At the moment there are no standardised criteria in determining whether the EU regulatory network incident management plan for medicines for human use should be initiated for supply shortages due to GMP non-compliance/quality defects.

The current document sets out a decision tree which would facilitate the decision on when such escalation to a European level could be considered.

#### **3. Decision tree**

##### **3.1 No escalation to European level is required if:**

- (a) Shortages are limited to a single member state (although noted that this situation may change over time);
- (b) The duration of the shortage is limited and not considered relevant from a clinical point of view (e.g. for vaccines, vaccination may be postponed for a few weeks), although this situation may evolve over time.

##### **3.2 Escalation to a European level may be considered if:**

- (a) The product is considered to be a critical medicinal product in a member state and there is evidence that indicates that the shortage will affect more than one member state. It is possible that there may be differential supply of GMP compliant/GMP non-compliant product between Member States;
- (b) A decision to keep a suspected defective product on the market may have possible safety implications (e.g. sterility is not guaranteed) that may indicate the need for union advice

on appropriate risk minimization measures to be taken to allow continued use of the suspected defective product;

- (c) The product at issue is considered to be non-critical but the concern is due to critical GMP non-compliance/quality defects which may affect other products on the union market;
- (d) The product is considered to be non-critical but shortages may have an impact on public health (e.g. owing to the number of users or the characteristics of the patient population).

Discussion should always take place on the lowest possible level and only be escalated for further discussion at European level in case there is an interest at Union level identified.

#### **4. Actions at Union level**

Once a member state or several Member States have decided that an escalation to Union level is necessary, the following principles should be followed in determining which committee at the agency should take the lead in the assessment and communication strategy. It is proposed that shortages only affecting centrally authorised products (CAPs) as well as shortages affecting both CAPs and non-CAPs are subject to the CHMP's review. Should more than one rapporteurship be affected, a lead rapporteur will be nominated by the committee. Should a shortage only affect non-CAPs, the member state(s) should escalate the issue to the CMD(h) for a harmonised response at Union level. PRAC will be consulted by the committees as necessary.

## Appendix 5

### Official Letterhead of the National Competent Authority.

#### 'Written confirmation' of API compliance, as defined in Article 46a(2)(b) of Directive 2001/83/EC

The competent authority of *[EU Member State]* wishes to advise the competent authority of *[third country]* that, following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC,

Company name:.....

Site address:.....

.....  
has been found to be **non-compliant** with standards of GMP equivalent to those laid down in Article 47 of Directive 2001/83/EC.

A statement of serious GMP non-compliance has been issued, which is appended to this notice.

*[Third country authority]* is requested to withdraw previously issued written confirmations of API compliance which fall within the scope of the statement of serious GMP non-compliance. Notification to *[name of supervisory EU authority]* when the manufacturer is considered to have restored compliance equivalent to EU GMP would be appreciated, to assist in scheduling a future EU re-inspection of the site.

Contact details for communications relating to this statement of serious non-compliance are as follows:

Inspection case reference:

.....

Name of responsible officer of the EU supervisory authority:

.....

Address:

.....

Telephone:

.....

Email:

.....

## Appendix 6: Supervisory risk assessment

### Notification by supervisory authority

Issued by:

Inspection reference:

Manufacturer name and address:

Introduction / background:

*Brief description of relevant information about the site and background information.*

*Include what the site is responsible for; what led to the inspection and what the outcome was. Include whether any previous inspections are relevant.*

Main inspection findings:

*Briefly describe the critical and major deficiencies that have led to the non-compliance statement being issued. Include sufficient detail for complete understanding but consider possible interpretation issues when describing deficiencies.*

*This section will typically contain more detail than the summary provided in section 3 of the Statement of serious GMP/GDP non-compliance template.*

*Consider that not everybody reading this information will have expert GMP/GDP technical knowledge.*

Concerned medicinal products (if known; list may not be exhaustive):

*Provide as much information as possible. Incomplete information should be identified as such.*

*Include (where relevant, and if known):*

- *strength(s) and presentation(s)*
- *pending applications, investigational products*
- *products authorised in other EU Member States*
- *Active substances and any CEPs or ASMFs affected*
- *EudraCT numbers*
- *Identity of other supervisory authorities in the case of medicinal or investigational medicinal products or active substances imported into the Union*
- *RMS(s) and the competent authority(ies) responsible for the marketing authorisation(s)*

*Indicate if MRA partners are likely to be affected.*

**Assessment of main inspection findings on concerned medicinal products:**

*Describe the impact of the identified GMP/GDP deficiencies on risk to product quality, safety or efficacy. An assessment of impact to clinical trial data validity should be made, if relevant to the GMP/GDP deficiencies (e.g. product mix-ups or failure to properly randomise / blind IMPs).*

*Have any mitigating actions already been implemented (either formally or informally)? An assessment of the consistent use and effectiveness of these mitigating actions should be provided.*

**Recommendations:**

*Any recommendations for action should be commensurate with risk. They should be stated in a manner that takes account of the interests of the Union as a whole, and permits flexibility in decision-making at national and Union level, taking into account product criticality.*

- *At the time of drafting, product criticality may not be known for all Member States. Recommendations should accommodate the possibility of critical products as further information becomes available.*

*Are there any recommendations towards other National Competent Authorities or EU Committees, for example:*

- *If it is believed that there is evidence or significant risk of defective product on the market, any recall recommendations to other Member States should usually be limited to 'consideration of recall following NCA assessment'. Where possible, agree this text with the authority leading quality defect assessments.*
- *Recommendations for prohibition of importation and/or supply*
- *Are NCA assessments required of the product's criticality in the Member States?*
- *Any recommendations for action against marketing authorisation(s) or clinical trial*

*The 'assessment of main inspection findings on concerned medicinal products' should provide supporting rationale to recommendations for interim urgent measures and final supervisory actions.*

*Recommendations are based on the information available at the time of writing, and may be updated in light of further information. Any amendments must be clearly highlighted.*

- **Interim urgent measures (if applicable):**

*Include any recommendations to maintain patient safety and/or avoid shortages of critical products in the interim period. This should include the rationale for these actions, with reference to the 'assessment of main inspection findings on concerned medicinal products'.*

*Recommendations for urgent actions may include recall or prohibition of supply of batches already imported into the Union, but not yet placed on the market.*

- **Final supervisory actions:**

*Include any SA proposals for action against EU manufacturing authorisations, or EU importation authorisations in the case of non-compliance at third country manufacturing sites*

*Any recommendations on final supervisory actions (e.g. action against marketing authorisation(s) or clinical trial authorisation(s)) should be stated in a manner which permits flexibility in decision-making*

*at national and Union level, taking into account product criticality. Avoid statements that can be interpreted as an instruction, such as "recommendation that MA should be suspended". Instead consider "action against affected MAs should be considered where potential quality defect has greater impact to public health than supply restriction in affected Member State(s)".*

**Impact on any other active substance manufactured at the same site / CEP considerations (if any):**

*If CEPs are impacted, ensure that this section is discussed and text agreed with EDQM. If action has not been agreed at the time of publication of the RRA, this can be noted as 'potential impact to CEPs remains under assessment'.*

**Implications for product supply based on information available to the supervisory authority:**

*At the time of drafting, product supply and/or criticality information may not be known for all products or Member States. Relevant available information and possible impact on supply following this inspection should be provided, e.g.:*

- *Quantity of materials/products available*
- *Number of batches in progress / completed / released*
- *Typical market usage*

**Information requested from affected Member States:**

*A summary of information requested from affected Member States should be listed.*

*This should be based on the requirements for assessment listed above.*

**Contact details for responses:**

**Deadline for responses:**

# Procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations

## Table of contents

1. Summary
2. Definitions
3. Principles
4. Scope
5. Procedure and responsibilities

<b>Title</b>	<b>Procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations</b>
Date of adoption	21 September 2021
Date of entry into force	9 months following publication
Supersedes	Version in force since November 2012
Reason for revision	Minor updates to reflect current practice
Notes	Not applicable



# 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 Union Procedures (CoUP) 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 Union 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 Union 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 regulatory 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 Union. It is possible that the detailed GMP non-compliances identified in the notification may have limited or no impact on EU products, e.g.:

Figure: 4. in cases where the issues relate to facilities or products which are not involved in EU supply, or;

Figure: 5. 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;

Figure: 6. 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 Union 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 regulatory action to be taken. Notification of GMP deficiencies which do not require regulatory action should be recorded in the relevant Supervisory Authority's model for risk based inspection planning, or compliance management, in accordance with CoUP.
- 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 Union 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 regulatory action applicable to the situation should be considered in accordance with the detailed guidance provided in CoUP.
- 4.2 Procedures should require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

Information shared by third country authorities may include situations where the GMP non-compliance does not reach the threshold of requiring regulatory action, and/or where measures equivalent to EU regulatory action are not proposed by the third country authority. In this case, the relevant national competent authority should review the notification. The necessary measures described under the risk-based inspection or compliance management procedures in the CoUP should be taken.

- 4.3 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.
- 4.4 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.
- 4.5 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 Union impact. Information to be collected 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 coordinating authority 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. Appendix 6 to the “Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health” and associated guidance notes may be used to structure requests for additional information.

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<sup>1</sup>.

5.1.4 If the third country authority notification refers to a site in a third country, the coordinating authority is responsible for dissemination to all EU Member States and EMA, using the rapid alert single point of contact (SPoC) list<sup>2</sup>. If the information falls only within the scope of ‘compliance management’, this should be provided to the EU Supervisory Authority only.

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).

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<sup>1</sup> Without prejudice to any confidentiality arrangements.

<sup>2</sup> Without prejudice to any confidentiality arrangements.

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:

<b>Product type</b>	<b>Coordinator</b>
Centralised Product	Supervisory Authority will lead; EMA will co-ordinate actions.
DC / MRP	Supervisory Authority / Reference Member State
National Authorisation	Member State granting authorisation
IMP	Member State granting CTA
API	Coordinator responsible for the product type containing the affected API(s)

- 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 using Appendix 6 to the "Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health" and associated guidance notes to determine the actions to be taken. Further guidance on the regulatory actions available for consideration is described in CoUP.
- 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 regulatory 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 regulatory 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 CoUP. 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 CoUP may be an appropriate alternative means to inform the decision regarding the issuance of a statement of serious GMP non-compliance.

# Guideline on training and qualification of inspectors performing inspections of wholesale distributors

## Table of contents:

1. Summary
2. Scope
3. Background
4. Qualification and training
5. Maintenance of competence
6. Harmonisation within the EEA
7. Legal references

<b>Title</b>	<b>Guideline on training and qualification of inspectors performing inspections of wholesale distributors</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	version adopted November 2010
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# **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<sup>1</sup> 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 Regulation 2019/6. 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. 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.

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<sup>1</sup> This includes compliance with Good Distribution Practice for medicinal products for human use and Good Distribution Practice for veterinary medicinal products.

### 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 Union 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 feed back 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.

# GDP inspection procedure

## Table of contents:

1. Introduction
2. Scope
3. General considerations on inspections
4. Inspection procedures
5. Inspection report
6. Inspection frequency
7. Inspection of brokers

<b>Title</b>	<b>GDP inspection procedure</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted June 2013
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# **GDP inspection procedure**

## **1. Introduction**

In accordance with Art 111 of Directive 2001/83/EC and 123 (1) of Regulation 2019/6 competent authorities are required to perform inspections of wholesale distributors and their premises and may also, for medicinal products for human use only, perform inspections of brokers. 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.

## **2. Scope**

This guideline defines the basic procedures to be followed by an inspector when preparing for and performing Good Distribution Practice inspections. It gives guidance on issuing an inspection report that should list and categorise all deficiencies found during the inspection. It describes the issue of a certificate when finalising the inspection. This document describes also how to establish the frequency of inspections.

## **3. General considerations on inspections**

The primary role of the inspector is the protection of public and animal health in accordance with Union provisions. The function of the inspector is to ensure adherence by wholesale distributors and brokers to GDP principles and guidelines and compliance with legislation.

The primary goal for the inspector should be to determine whether the various elements within the quality management system are effective and suitable for achieving compliance with GDP principles.

Inspectors should strive to create a positive atmosphere during the inspection. The inspector should be aware of his/her influence in decision making processes. The inspector should always answer questions but avoid entering the role of a consultant.

Different types of inspection may be carried out according to the activities of the company. The conduct of an inspection may vary according to its objectives and may for example focus on the general level of GDP compliance, or on a particular activity covered by the wholesale distributor.

GDP inspections may be performed before granting or modifying a wholesale distribution authorisation. Routine GDP inspections cover the assessment of GDP compliance of a site. Non-routine inspection may be conducted to check specific aspects of GDP compliance, for example investigation of complaints, recalls, quality defects, previous non-compliance or suspected falsified products.

The wide diversity of facilities together with the variety of products supplied and handled by a site means that assessment by inspectors on site of the degree of compliance with GDP is essential. A consistent approach to the evaluation of the GDP standard is required.

Inspections may disturb the normal working patterns within a company and inspectors should therefore carry out their inspection in a careful and planned manner. Inspectors should be aware of the confidential nature of their work.

## 4. Inspection procedures

### 4.1 Planning of Inspections

The competent authority should plan inspections in advance and elaborate a programme. This programme should ensure that the frequency of inspection of individual wholesale distributors can be adhered to as planned. Sufficient and qualified resources must be determined and made available to ensure the designated programme of inspections can be carried out in an appropriate manner.

### 4.2 Preparation of Inspections

Prior to conducting an inspection, the inspector should familiarise him/herself with the company to be inspected according to the inspectorate's procedures. This may include the following:

Figure: 1. Review of documents requested prior to the inspection;

Figure: 2. Review of the activities conducted by the company and types of products authorised under the wholesale distribution authorisation of the company (may include internet search about the company);

Figure: 3. Review of reports from previous inspections and other records available;

Figure: 4. Review of responses (follow-up actions) as committed to by the company arising from deficiencies identified during previous inspections;

Figure: 5. Review of product recalls and suspected falsified medicinal products since the previous inspection;

Figure: 6. Review of any specific standards/guidelines associated with the site to be inspected (e.g. internal Inspectorate guidelines).

Plan the areas to be covered during the inspection and where considered appropriate, prepare a written plan. In the case of an inspection team, the lead inspector shall coordinate these activities, delegating the inspection preparation activities as he/she considers appropriate.

The inspection plan may include:

Figure: 7. The objectives and scope of the inspection in light of previous inspections;

Figure: 8. Identification of the inspection team members and their respective roles;

Figure: 9. Identification of the organisational units to be inspected;

Figure: 10. The expected time and duration for each major inspection activity (premises and equipment, personnel etc.);

Figure: 11. The schedule for the close-out meeting.

### 4.3 Announcement of inspection

Competent Authorities have the right to inspect at any time. Prior announcement of inspection may be given. By informing in advance the day(s) for the inspection to take place and the length of time the inspector expects to be on site, the objectives of the inspection will be known to the company and the relevant personnel and documentation can be made available.

### 4.4 The opening meeting

Request an opening meeting with the management and key personnel of the company to introduce yourself and any accompanying official(s) or specialist(s) and to discuss general details of the inspection plan. Immediate site tour upon arrival may be of value in some cases, particularly where the inspection is unannounced.

During the opening meeting the inspector should:

Figure: 12. outline the purpose and scope of the inspection;

Figure: 13. identify of any hazards on site;

Figure: 14. review previous inspection issues and outstanding corrective / preventative actions;

Figure: 15. identify the activities of the company including significant changes since the last inspection;

Figure: 16. inform the company of the documentation which may be required during the inspection;

Figure: 17. if considered appropriate to the inspection request a rapid initial site tour for familiarisation with the site.

During the opening meeting the company should:

Figure: 18. present the management structure and quality management within the company;

Figure: 19. explain significant changes in premises, equipment, products and personnel since the last inspection;

Figure: 20. identify personnel to accompany the inspector and allocate a room to review documentation if requested.

#### 4.5 The inspection

During the inspection, always discuss observations as they arise to establish facts, indicate areas of concern and to assess the knowledge and competence of personnel.

A detailed plant tour may be performed to determine whether the facilities and equipment are of suitable lay-out and design and whether the way in which these are used suits the intended operations. Normally, for the first inspection of a site, the logical flow of products is followed.

It may be appropriate to concentrate effort in one department of the company if there are special problems or requirements.

The system of documentation, based on procedures and records covering the distribution operations should be checked by examining particular examples at different stages throughout the receipt, storage, assembly and dispatch process.

In order to assess compliance with the terms and conditions of the wholesale distribution authorisation the following documentation may be examined:

Quality management system related documentation:

Figure: 1. standard operating procedures (SOPs);

Figure: 2. job descriptions and personnel training records;

Figure: 3. supplier and customer qualification records;

Figure: 4. contract agreements for outsourced activities;

Figure: 5. system for handling a suspected falsified medicinal products;

Figure: 6. deviations from standard processes;

Figure: 7. suitability of premises.

Documentation of ongoing activities:

Figure: 1. review of actual operating activities and changes;

Figure: 2. review of supply chain;

Figure: 3. check of invoices correlating to supply chain;

Figure: 4. temperature and humidity monitoring of storage areas;

Figure: 5. verification of effectiveness of low temperature storage facilities;

Figure: 6. returned product log;

Figure: 7. records of product quality complaints;

Figure: 8. records of product recalls and mock recalls;

Figure: 9. self-inspection system and execution;

Figure: 10. review records related to transportation.

Wholesaler distributors may be inspected with regard to their capability to maintain the minimum stock of life saving medicinal products according to national law. Their internal procedures to be on stand-by in case of emergency should be critically reviewed.

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 but these discussions should not delay the progression of the inspection.

In the case where serious deficiencies leading to possible risk for the patient/animal and public or animal health are identified, immediate action should be taken. These actions may include requesting the company to complete any of the following:

Figure: 1. Voluntarily suspending the wholesale distribution activities/operations impacted (e.g. supply of products requiring low temperature storage);

Figure: 2. Quarantining and withholding from sale, supply or export any batches of medicinal products impacted;

Figure: 3. Initiating the recall of impacted batches of medicinal products that have already been sold, supplied or exported.

The inspector should ensure, where appropriate, that these restrictions have been implemented by the company prior to completing the inspection. This should include obtaining written statements to this effect from the appropriate personnel. This should also include commitment that the restrictions will remain in place, until the underlying deficiencies have been addressed to the satisfaction of the competent authority.

Throughout the inspection, review:

Figure: 1. The completeness of the inspection with respect to the original objectives;

Figure: 2. Conduct of the inspection with reference to the areas covered / not covered;

Figure: 3. Classification of deficiencies and inter-related deficiencies which may be indicative of a system failure rather than isolated incidents.

Ensure that deficiencies are discussed during the course of the inspection so that an inordinate amount of time is not taken up with discussion at the final close out meeting.

#### 4.6 The close-out meeting

The close-out meeting is a significant part of the inspection. Summarise and classify the findings of the inspection in the close-out meeting with representatives of the company. Senior management of the company should be present, where appropriate. Discuss the deficiencies observed during the inspection and their classification. Where considered necessary, discuss deadlines for remedial actions.

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.

Assess the need for a follow-up inspection based on the nature of the deficiencies observed. The company should be informed at this stage of the possible need for a follow-up inspection. In certain cases, it may be appropriate to evaluate the responses received from the company before determining if a follow up inspection is required.

In certain cases of critical non-compliance further actions may be taken against the authorisation holder or broker by the competent authority.

## 5. Inspection report

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 GDP certificate within the statutory 90-day timeframe.

A response with proposed corrective actions should be requested to be returned by the company in due course. These corrective actions and proposed timelines for their implementation should be considered by the inspector and a decision made on whether the entity can be considered to be compliant with GDP.

The close out of the inspection should be completed within 90 days from the last day of inspection in order to issue a certificate of good distribution practices to the inspected entity if the outcome of the inspection shows that it complies with GDP. If the inspection outcome was negative, a statement of non-compliance should be issued and regulatory actions should be considered.

The GDP certificate or the non-compliance statement shall be entered in the Union database referred to in Article 111(6) of Directive 2001/83/EC and Article 91(3) of Regulation 2019/6..

Inspection reports should ideally be subject to a review process, which may include:

Figure: 1. extent and depth of inspection;

Figure: 2. classification and description of deficiencies;

Figure: 3. actions required and timelines proposed for completion;

Figure: 4. clarity and relevance of the content of the report.



## 6. Inspection frequency

Inspections should be carried out repeatedly to ensure compliance with GDP by the wholesale distributor and the authorised premises. The intervals between inspections should be set at a level that provides confidence that the wholesale distributor maintains continued compliance with GDP and its principles. The maximum period between inspections per site should not exceed 5 years as lack of continuity may give rise to lower awareness of current GDP or allow significant deficiencies to develop.

The activities of the individual company and its past record of GDP compliance should be taken into consideration when planning the frequency and duration of inspection. A risk based approach may be applied to establish the frequency of inspections.

Factors that could be taken into account to establish the interval between inspections might include:

Figure: 1. Size of site and number of staff;

Figure: 2. Number of customers / sales volume;

Figure: 3. Number of suppliers, type / category of supplier (special medicines);

Figure: 4. Parallel distribution/ parallel trade / import;

Figure: 5. Exporter to non-EU and complexity of the supply chain;

Figure: 6. Handling of products requiring low or high temperature storage;

Figure: 7. Contract activities;

Figure: 8. Categories of products - narcotics /non-authorised medicines in EEA / non-authorised medicines in country of company;

Figure: 9. Previous inspection history and compliance with GDP;

Figure: 10. Number and relevance of any areas not covered at previous inspection;

Figure: 11. Number and type of deficiencies found on previous inspections;

Figure: 12. Company corrective actions proposed following previous inspections;

Figure: 13. Complaints history, number and criticality of complaints.

The risk based approach may be used to set an inspection frequency but the date of inspection should be reviewed if significant issues are reported to the competent authority. Such issues could be staff changes, complaints, recalls, quality defects, reports of suspected falsified medicines.

Inspections in the context of granting a Wholesale Distribution Authorisation should be determined on a case by case basis.

## 7. Inspection of brokers (medicinal products for human use only)

Inspections may also take place at the premises of brokers of medicinal products for human use. These inspections would usually be for-cause inspections to investigate a suspected non-compliance with legislation and the specific provisions for brokers in the Union Guidelines on GDP. The need for an inspection could for example be identified during inspections of wholesale distributors operations or could be triggered by the following:

Figure: 1. Suspicion of brokering of falsified medicinal products;

Figure: 2. Suspicion that the broker is not located in address to which it has registered;

Figure: 3. Suspicion that they may be conducting activities of a wholesale distributor;

Figure: 4. Suspicion of brokering between unauthorised suppliers / customers;

Figure: 5. Suspicion that paperwork conceals the true origin or destination of the product.

The inspection of a broker should be carried out in accordance with this procedure.

# The issue and update of GDP certificates

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1. Introduction
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3. When GDP certificates should be issued and Union database entry
4. Non-compliance with GDP
5. Renewal and update of GDP certificates
6. Closure of wholesale distribution site

<b>Title</b>	<b>The issue and update of GDP certificates</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted June 2013
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# The issue and update of GDP certificates

## 1. Introduction

Article 111(5) of Directive 2001/83/EC requires a certificate of Good Distribution Practice to be issued to the wholesale distributor of medicinal products for human use within 90 days of carrying out an inspection if the outcome of the inspection shows that the wholesale distributor complies with the principles and guidelines of Good Distribution Practice as provided for by Union legislation. The GDP certificates issued or the information indicating that a wholesale distributor does not comply with GDP, shall be entered into the Union database as required under Article 111(6) of Directive 2001/83 EC.

Regulation 2019/6 does not explicitly require to issue a certificate of Good Distribution to the wholesale distributor of veterinary medicinal product within 90 days of carrying out an inspection if the outcome of the inspection shows that the wholesale distributor complies with the principles and guidelines of Good Distribution Practice. However, wholesale distributor shall verify that the supplier complies with good distribution practice for veterinary medicinal products through information obtained from the national competent authorities or the Union database on manufacturing, import and wholesale distribution referred to in Article 91(1) of Regulation (EU) 2019/6. In this context, Competent Authority willing to issuing GDP certificates may follow this procedure.

The requirement applies regardless as to whether the inspections are unannounced or routine.

This document is intended to give interpretation on aspects of responsibilities of the issue, renewal and update of GDP certificates.

## 2. Use of certificates

GDP certificates are for the purpose of confirming to a wholesale distributor the overall conclusion of an inspection with respect to compliance with GDP. Within the EEA they do not replace confirmation of the holding of a wholesale authorisation.

## 3. When GDP certificates should be issued and union database entry

### 3.1 Responsibility for issue of GDP Certificates

Responsibility for issuing GDP certificates and placing entries into Union database rests with the competent authority.

Following each relevant inspection, a report in accordance with the Union format should be produced by the responsible inspector, which should contain a clear statement as to whether or not the wholesale distributor complies with the principles and guidelines of GDP as provided for in Union legislation.

Where this is the case, within 90 days of the last day of the inspection concerned, the competent authority should issue a GDP certificate in accordance with the Union format to the wholesale distributor that underwent the inspection.

In the case of non-compliance see the relevant Union 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 GDP certificates may be issued in response to a request from the wholesale distributor.

### **3.2 Circumstances where the issue of a certificate to a wholesale distributor may not be applicable (other than in cases of failure to comply with GDP)**

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

It may not be appropriate to issue a GDP certificate following an inspection in response to an application for, or variation to a wholesale 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 wholesale distributor should be informed of this beforehand.

### **3.3 Scope of individual certificates**

The certificate should include all operations deemed to be GDP compliant as a result of the inspection.

For ease of database entry and to reduce the use of free text, the Union database contains standard phrases to cover the most common situations.

### **3.4 Responsibility for Union database entry**

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

## **4. Non-compliance with GDP**

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

## **5. Renewal and update of GDP certificates**

5.1 A **certificate** itself is not renewed, as it is a declaration of the status of GDP 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 Union database however require a different approach.

Union database 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.

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**

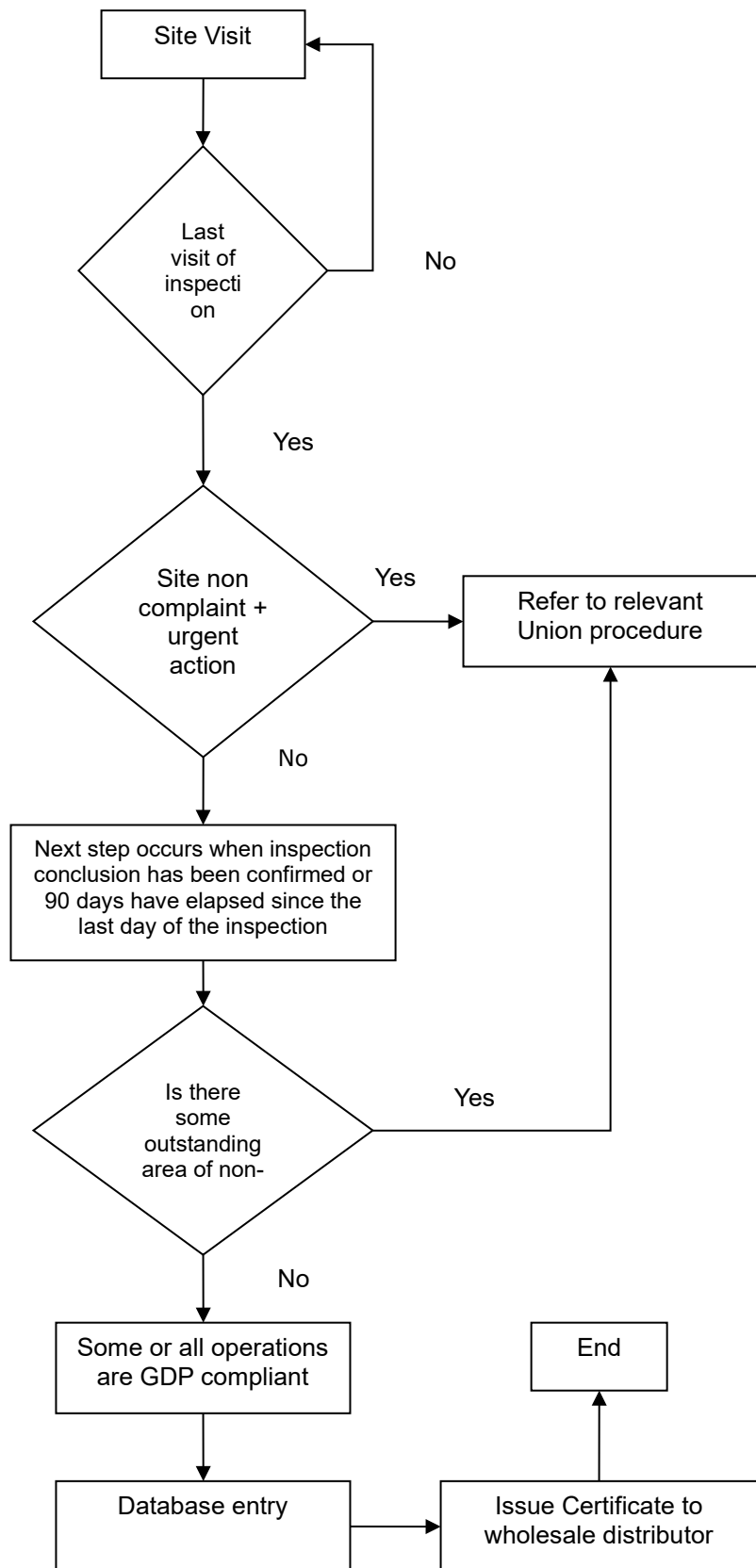
An updated certificate may be issued to a wholesale distributor and input into Union database by the authority that issued the last certificate at the request of a wholesale distributor when administrative changes occur that affect the details appearing on the certificate and where the competent authority agrees that a re-inspection is not required. An example would be a change in the name of the wholesale distributor. 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 wholesale distribution site**

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

]

# Appendix 1



# Co-ordinating GMP inspections for centrally authorised products

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5. Pre-submission notification by the applicant for a marketing authorisation
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<b>Title</b>	<b>Coordinating GMP inspections for centrally authorised products</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted August 2010
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable



# 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) of Regulation 726/2004 of the European Parliament and the Council and 94 (4) of Regulation 2019/6.

Repeated (routine re-inspections) may also be requested according to the provisions of Articles 19(3) of Regulation 726/2004 of the European Parliament and the Council and 94 (4) of Regulation 2019/6.

## 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 of Regulation 726/2004 and Articles 123 (1) and 7 of Regulation 2019/6.

**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 Union 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 Union 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 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)rappporteur 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)rappporteur 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 Union 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)rappporteurs, 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 by EMA.

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 Union legislation and to update the EudraGMDP database accordingly.

# Procedure for compliance management

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4. Procedure
5. Communication of compliance management measures with relevance to other national competent authority's risk based inspection programmes
6. Closure of compliance management cases

<b>Title</b>	<b>Procedure for compliance management</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Procedure for compliance management

## 1. Principle

In light of Article 111 of Directive 2001/83/EC, and Article 63(4) of Regulation 536/2004 and Article 123 of Regulation 2019/6, the compliance with the GMP and GDP principles should be verified by the means of inspections. If the outcome of the inspection shows that the inspected entity complies with principles of GMP and GDP, a compliance certificate shall be issued (Article 111(5) of Directive 2001/83/EC and article 94 (1) of Regulation 2019/6). In case of non-compliance of a site with principles of GMP or/and GDP, a statement of non-compliance shall be introduced to the EudraGDP base (Article 111(7) of Directive 2001/83/EC and article 94 (2) of Regulation 2019/6).

To ensure a continuous supply of quality medicines for human and veterinary use, it is in the interest of patients, animals, industry and regulators to take proactive action to address deficiencies in compliance with Good Manufacturing and Distribution practices as published by the European Commission in Eudralex Volume 4.

It is understood that a manufacturer or distributor can be considered to be in general compliance even if deficiencies requiring an improvement were identified, which the national competent authority is satisfied can be resolved in order to protect public or animal health. Action following the discovery of any of those issues should be commensurate with the level of risk posed.

The primary intention of early intervention (in the context of this procedure, 'administrative action') is to enable the company to ensure satisfactory compliance before regulatory action becomes necessary. However, in cases of continued non-compliance where this proactive approach is not yielding the required improvements, regulatory action may be considered.

Compliance management is appropriate in situations where the identified issues may not be effectively managed in the short term through a national competent authority's routine inspection process, especially in cases where it is considered that regulatory action (such as issuing statements of non-compliance or suspension of manufacturing / wholesale distribution authorisations) may not be necessary at that time. It is implemented independently by the national competent authority, and operates within the boundaries of the risk based inspection (RBI) process, with a view to avoiding the necessity of regulatory action by:

Figure: 1. Communicating the escalating compliance concerns to manufacturing / distribution authorisation holders and/or marketing authorisation holders.

Figure: 2. Developing a case management strategy to direct the site towards a state of satisfactory compliance, or (in the event of continued non-compliance) to gather evidence in preparation for consideration of regulatory action.

Manufacturers and distributors who are supervised through the compliance management process must be considered by the national competent authority to generally meet the rules governing medicinal products in the European Union which ensure the protection of public and/or animal health. Serious non-compliance by definition requires regulatory action to protect public or animal health to be taken

without delay, in accordance with the Compilation of Union Procedures referring to serious GMP and GDP non-compliance.

The compliance management process does not replace or amend the regulatory actions described within EU medicines legislation at Union level, the Compilation of Union Procedures, and the equivalent provisions at national level in each Member State. It is not necessary for consideration of regulatory action to be preceded by the compliance management process. However, continued GMP and/or GDP deficiencies during the compliance management process may subsequently lead to consideration of regulatory action.

## 2. Definitions

**'Administrative action'** is defined as:

Measures taken by the national competent authority which do not result in regulatory action.

**'Regulatory action'** is defined as:

Action (suspension, compulsory variation or revocation) taken against the holder of a manufacture/import authorisation, wholesale distribution authorisation, active substance registration, or marketing authorisation; publication of a statement of GMP or GDP non-compliance; or disciplinary measures taken against a named person (e.g. Qualified Person or Responsible Person) as a result of serious GMP or GDP deficiencies.

**'Compliance management'** is defined as:

The use of inspection and non-inspection monitoring measures to proactively manage manufacturing, importation and wholesale authorisation holders and manufacturers of active substances demonstrating deficiencies in GMP/GDP compliance or other risk indicators, when it is considered that routine inspection may not be effective in achieving compliance improvements within a satisfactory time period.

**'Serious' GMP / GDP non-compliance** is defined as:

Non-compliance with GMP / GDP that in the opinion of the reporting inspectorate is of such a nature that regulatory action should be considered to remove a potential risk to public or animal health in accordance with national legislation and Compilation of Union Procedures for serious non-compliance.

## 3. Scope

The administrative actions described in this SOP are applicable to all GMP and GDP inspections whether in the territory of the national competent authority or in third countries, including inspections requested by the manufacturer, importer, the European Commission, the European Medicines Agency (EMA) or the European Directorate for the Quality of Medicines and Healthcare (EDQM). The procedure defines the administrative actions taken by the national competent authority following inspection of regulated activity/premises where GMP/GDP deficiencies require intervention to escalation of compliance concerns to authorisation holders for immediate attention if regulatory action is to be avoided. These administrative action principles are flexible in their application, to prevent conflict with national legislation in each Member State, and to permit compliance management to be commensurate with the specific deficiencies identified.

References within this SOP relating to action against Marketing Authorisations or Manufacturing / Import Authorisations are equally applicable to IMP dossiers submitted as part of a CTA, and MIA (IMP)

authorisation holders. Marketing authorisation holders and clinical trial sponsors should also be considered synonymous for the purposes of this SOP.

References within this SOP relating to 'national competent authority' should be considered synonymous with 'EU supervisory authority' where compliance management is implemented following an inspection in a third country.

## 4. Procedure

This procedure describes the principles of compliance management which are designed to integrate with the risk-based inspection procedures of each national competent authority.

General GMP / GDP deficiencies should be managed within the risk based inspection process in the first instance. Compliance management is appropriate in situations where increased frequency of inspections is considered not to be effective in achieving compliance improvements within a satisfactory time period.

### 4.1 Identification of unsatisfactory compliance requiring compliance management

The compliance management process in response to chronic or significant GMP / GDP deficiencies is usually initiated by an Inspector's recommendation, and continues with an internal review procedure in order to decide whether to support the recommendation, or whether alternative action is more appropriate.

Thresholds for initiating compliance management should be determined by the national competent authority. Examples include:

Figure: 1. Evidence of poor compliance history, for example:

Figure: 2. Number of major deficiencies;

Figure: 3. Repeated major deficiencies issued in successive inspections;

Figure: 4. Non-compliance with previous commitments to critical or major deficiencies.

Figure: 5. Unsatisfactory response to an inspection, for example:

Figure: 6. Failure to provide a response to inspection deficiencies;

Figure: 7. Unacceptable proposals for corrective and/or preventive action for major deficiencies;

Figure: 8. Unacceptable timescale for interim corrective actions or final preventive actions.

Figure: 1. The site requires direction and encouragement in achieving compliance by raising awareness of GMP / GDP obligations at a senior level (e.g. in future projects where the inspector believes there is significant risk of failure due to inadequate resourcing or planning by the company).

Any recommendation for regulatory action against a manufacturing or marketing authorisation (or refusal to grant an authorisation), regulatory action against a person named on an authorisation (e.g. Qualified Person) or recommendations for issuing a statement of non-compliance against one or more site activities must be managed within the procedures for serious GMP/GDP non-compliance described

within EU medicines legislation at Union level, the Compilation of Union Procedures, and the equivalent provisions at national level in each Member State.

## **4.2 Supervision of manufacturers / distributors under compliance management principles (administrative actions)**

Compliance management will vary depending upon the specific compliance issues identified. Inspection and non-inspection monitoring measures, or administrative actions such as communication of the national competent authority's concerns to the authorisation holder senior management and conditioned (restricted) approvals may be used alone or in combination.

The rationale for administrative action, together with the case management strategy (including criteria for further escalation for regulatory action) should be documented within the national competent authority's inspection record. This must include objective compliance-indicating measures, in order to assess progress over time.

### **4.2.1 Risk based monitoring**

Risk based monitoring measures with frequency and scope relevant to the national competent authority's concerns may be utilised. These include inspection measures, written progress updates and reporting of metrics to provide indicators of either progress with remediation plans and improving compliance, or further deficiencies which require consideration of regulatory action.

#### **4.2.1.1 Inspection measures**

Re-inspection frequency and scope should be applied in accordance with the existing risk based inspection process. Compliance management input to inspection planning should ensure:

Figure: 1. Particular attention to the issues which resulted in the escalation for compliance management and evidence of progress with remediation, particularly in situations where the agreed corrective action plan is anticipated to continue for an extended period of time;

Figure: 2. Continued awareness of the overall inspection coverage for the manufacturer / distributor, to ensure that focus on specific areas of concern does not result in omission of other site activity inspections.

It may be possible to make optimum use of inspectorate resources by adjusting the normal risk based inspection interval on the basis of non-inspection monitoring measures such as periodic written updates or submission of metrics.

#### **4.2.1.2 Written updates and reporting of metrics**

The authorisation holder's progress with corrective actions may be monitored between on-site inspections via remote assessment, where defined and appropriate. Care should be taken to ensure that the frequency of update submissions is commensurate with compliance concerns, and do not impede the organisation's progress with implementing their remediation plan.

Examples of written updates include:

Figure: 1. Periodic submission of the agreed action plan, demonstrating compliance with the proposed actions and completion dates;



Figure: 2. Reports from authorisation holder investigations into the specific compliance failures identified, and corrective actions arising;

Figure: 3. Evidence of continued senior management support to the remediation plan (e.g. high level progress reports signed by senior management, confirmation of adequate financial and personnel resources);

Figure: 4. 'Exception reports' submitted by the authorisation holder to notify the national competent authority of non-compliance with previously agreed action plans (e.g. delays in completing action), or identification of additional deficiencies as a result of further investigation work.

Metrics reporting may also be used as evidence of effective remediation. The metrics should be carefully selected to be specific and compliance-indicating, taking into account NCA resources and the GMP/GDP concerns which resulted in compliance management measures. For example, metrics relating to 'on time' stability sample analysis may be used as an indicator of improved management and resourcing of a previously deficient on-going stability programme.

The national competent authority should request the reporting of negative compliance indicators as well as positive indicators, as this ensures transparency in communication, facilitates the continued review of risk-benefit decisions by the national competent authority, and also informs the planning of future re-inspections. Metrics should be selected with care to avoid a perception that the NCA is taking over the responsibility of the manufacturer/ distributor.

#### **4.2.1.3 Market surveillance measures**

Increasing regulatory oversight may include market surveillance sampling and testing of the company's products where relevant to the identified areas of concern. The national competent authority may also request increased level of quality defect reporting as an additional surveillance measure during a period of compliance management.

Such measures can supplement and support inspection-related activities.

#### **4.2.2 Administrative action: 'Cautionary letters' – outlining compliance concerns and future regulatory actions if improvements are not made**

'Cautionary letters' may be written to the manufacturer / distributor or marketing authorisation holder to outline specific compliance concerns, relevant company history, and the potential consideration of regulatory action in the event of continued GMP and/or GDP deficiency. Where appropriate, specific measures or milestones for future compliance assessment should be described.

Cautionary letters may be formatted in accordance with existing regulatory authority procedures for communicating with manufacturers, distributors and marketing authorisation holders. Consideration should be given to public visibility of cautionary letters where legislation permits. Where required, confidentiality requirements should be adopted.

The national competent authority will assess responses to cautionary letter(s). The outcome of this assessment should be considered when making decisions on the case management strategy and should follow a defined process.

##### **4.2.2.1 'Cautionary letter' to the manufacturer / distributor**

Letters may make specific reference to routine obligations already imposed upon authorisation holders (e.g. ensuring only certification of product which is in compliance with its MA), but should not inform the company of specific corrective or preventive actions to address deficiencies. Letters should be signed by a senior person of the NCA who is not involved with the site inspection, as this further emphasises the nature and severity of compliance concerns.

Letters sent to the inspected manufacturer or distributor may be addressed to the Qualified Person or Responsible Person. In situations where the national competent authority believes that site senior management is not receiving relevant information from the Qualified Person or Responsible Person, or that they are not providing adequate oversight and support to ensuring compliance, the letter may be addressed to the site senior management. In the case of a large organisation, the letter may be addressed to senior corporate management. A response to this letter should be requested by the national competent authority.

The messages communicated in the letter to the Qualified Person, Responsible Person, or senior / corporate management will vary depending on the specifics of each case. Points to consider include:

Figure: 1. Reminding the manufacturer / distributor of their obligation to ensure that products are manufactured / distributed in compliance with EU GMP / GDP;

Figure: 2. Reminding the manufacturer of its obligation to ensure that products are manufactured in compliance with the relevant marketing authorisation(s);

Figure: 3. A request for the manufacturer's / distributor's assessment of the causal factors leading to the observed poor compliance observed during inspection;

Figure: 1. A request for senior management proposals to ensure an appropriate and suitably resourced plan to ensure that the manufacturer / distributor will be in compliance with EU GMP/GDP at the next inspection;

Figure: 2. Reminding the manufacturer / distributor of potential future escalation of regulatory actions caused by a non-compliance with GMP/GDP, which may include action against their authorisation, and/or issuance of a statement of non-compliance;

Figure: 3. A request to provide specific metrics or periodic written updates (as outlined in section 4.2.1.2);

Figure: 4. Reminding the manufacturer / distributor that an increased inspection frequency is anticipated until acceptable compliance is demonstrated;

Figure: 5. A request that the manufacturer or distributor should also inform all contract givers, including the MAH, of the compliance situation. The NCA should have visibility of these communications to ensure that they are accurate and complete.

#### **4.2.2.2 'Cautionary letter' to the marketing authorisation holder**

In situations where the national competent authority believes that the MAH has insufficient visibility of the inspected site compliance issues, or where MAH actions may be required to facilitate improvement and/or reduce the risk of supply disruption, a cautionary letter may also be sent to the MAH.

Consideration should be given to confidentiality provisions between the NCA and the inspected site prior to sending a cautionary letter to the MAH. Notification of the MAH by the inspected site (see section 4.2.2.1) may facilitate subsequent direct communication between the NCA and MAH, following national regulations.

The messages communicated in the letter to the MAH will vary depending on the specifics of each case. Points to consider include:

Figure: 1. Reminding the MAH of their obligation to ensure that products are manufactured in compliance with EU GMP and the marketing authorisation;

Figure: 2. A request for the MAH's assessment of the causal factors leading to the observed poor compliance history, including their oversight of manufacturing and/or distribution activities;

Figure: 3. The MAHs assessment of the inspection findings and their future plan to ensure that the manufacturer / distributor will be in compliance with EU GMP/GDP in an appropriate period;

Figure: 4. Reminding the MAH of potential future escalation of regulatory actions caused by the inspected site's non-compliance with GMP/GDP, which may include consequential action against the marketing authorisation;

Figure: 5. Request for the MAH's contingency measures in the event of a future supply disruption caused by a non-compliance with GMP/GDP;

Figure: 6. Reminding the MAH that increased frequency of inspection of the manufacturer / distributor is anticipated until acceptable compliance is demonstrated.

To ensure visibility of impacted products, the manufacturer should be requested to provide a list of all EU marketing authorisation numbers and MAH contact details.

The inspecting authority may liaise with the authority responsible for issuing the marketing authorisation regarding the content of cautionary letters to MAHs, when appropriate. In the case of cautionary letters relating to EMA-requested inspections for centrally authorised products (CAPs), EMA should be consulted. For inspections of relevance to CAPs conducted in the territory of a national competent authority, the periodic update outlined in section 5 of this procedure may fulfil this requirement.

#### **4.2.3 Administrative action: Conditioned approvals (compliance-related GMP / GDP certificate restrictions, where no statement of non-compliance is proposed)**

In order to reduce compliance risk at a manufacturer or distributor pending completion of corrective actions, it may be desirable for the national competent authority to condition a GMP or GDP certificate to add further short term regulatory controls.

Conditions may relate to restrictions such as:

Figure: 1. **Capacity**, e.g. 'GMP certificate cannot be used to support new marketing authorisation applications or variations';

Figure: 2. **Facilities or equipment usage**, e.g. 'EU approval is limited to production rooms x, y and z, pending improvement in cross contamination controls';

Figure: 3. **Reduced period of certificate validity**, e.g. 'GMP certificate is valid for 1 year from the date of inspection. After this time, continued validity should be confirmed with the issuing authority';

Figure: 4. **Change management**, e.g. 'In view of the potential for ineffective change management, existing post-approval change management plans may not be implemented from the date of issuing this certificate. Applications involving this site for new post-approval change management protocols should not be approved'.

Restrictions placed on a GMP or GDP certificate as a result of compliance management should be relevant to the specific compliance concerns, and periodically reviewed to confirm their continued suitability.

Communication of compliance restrictions with relevance to marketing authorisation dossier assessment should be visible to pharmaceutical assessors across the Union via the GMP certificate. Where confidentiality requirements prevent publication of these restrictions, they should be mentioned on the GMP certificate as a restriction comment visible to registered EudraGMDP users. In situations where a cautionary letter has been issued to the manufacturer or distributor, this should be mentioned on the GMP certificate as a restriction comment visible to registered EudraGMDP users.

In order to ensure transparency of increased regulatory scrutiny, the following statement should be included on the certificate in public view:

Figure: 1. 'GMP certificate issued with administrative action(s) described within the procedure for compliance management in the Compilation of Union Procedures'.

## **5. Communication of compliance management measures with relevance to other national competent authority's risk based inspection programmes**

While compliance management is implemented by individual national competent authorities, it is beneficial for national inspectorates to have visibility of organisations under compliance management in one or more Member States.

Compliance management may be of relevance to more than one site in a multinational organisation. This may therefore impact the risk based inspection programmes of different EU national competent authorities, EMA and EDQM. To provide visibility to other national competent authorities, the planning module of EudraGMDP should be updated accordingly if the re-inspection of the site is changed as a result of compliance management activity.

Each national competent authority should make available information on sites under compliance management (organisation name and address) to other national competent authorities by providing searchable information in EudraGMDP for registered users. Inspectorates with an interest in one or more organisations identified should revert to the relevant national competent authority for further information under the existing EU exchange of information arrangements.

It should be remembered that a manufacturer or distributor under compliance management will, by definition, be considered by the national competent authority to remain acceptable for continued supply to the EU market, and will be in possession of a current GMP or GDP certificate. Member states should therefore consider information on compliance management sites as an intelligence input to risk based inspection planning, not as sites considered to be non-compliant and requiring immediate regulatory or market actions.

## **6. Closure of compliance management cases**

Following a period of compliance management, a manufacturer or distributor may be found to have returned to a state of acceptable compliance, or may have failed to implement the required improvements to a level where regulatory action should be considered.

Closure of compliance management cases should be indicated by updating EudraGMDP accordingly. In addition, the national competent authorities that requested information in accordance with section 5 should be informed whether sites have returned to routine inspection because of improvements or whether regulatory action is being taken.

Manufacturers and distributors who on subsequent inspection are found to demonstrate serious non-compliance with GMP or GDP will also be notified to national competent authorities via rapid alert following publication of a statement of non-compliance, in accordance with the Compilation of Union Procedures referring to serious GMP and GDP non-compliance.

### **6.1 Manufacturer / distributor has returned to acceptable state of compliance**

Following a period of increased monitoring (see section 4.2.1), if a manufacturer has achieved the required level of compliance, the compliance management case may be closed. Routine supervision of the site will return to the inspectorate's routine inspection programme. It is conceivable that the site will retain a high risk rating within the RBI system until consistent compliance with EU GMP/GDP has been confirmed.

The return to the routine surveillance process should be notified to the manufacturer / distributor by the national competent authority.

### **6.2 Manufacturer / distributor has not achieved acceptable state of compliance**

If the manufacturer / distributor fails to demonstrate the required improvements, or if compliance continues to deteriorate, the national competent authority should escalate the case for consideration of regulatory action. Evidence gathered during the period of increased monitoring (see section 4.2.1) may be used to support the proposal.

Recommendations for regulatory action should generally be supported by findings from a recent (typically less than 3 months previous) site inspection. This is to ensure that (i) indicators of declining compliance from desk-based review can be verified, and (ii) opportunities for legal challenge of subsequent regulatory action are minimised.

The escalation for consideration of regulatory action should be notified to the manufacturer / distributor by the national competent authority.

# EU/EEA Programme for Maintenance of Equivalence in Supervision of Good Manufacturing Practice Compliance of Pharmaceutical Companies

## Table of contents:

- Introduction
- Purpose
- Scope
- Definitions
- Components of the maintenance programme
- Maintenance Dossier
- Oversight

<b>Title</b>	EU/EEA Programme for Maintenance of Equivalence in Supervision of Good Manufacturing Practice of Pharmaceutical companies.
Date of adoption	May 2023
Date of entry into force	9 months following publication
Supersedes	n/a
Reason for revision	New procedure
Notes	Not applicable

# EU/EEA Programme for Maintenance of Equivalence in Supervision of Good Manufacturing Practice (GMP) Compliance of Pharmaceutical Companies

## 1. Introduction

When accessing as a new Member State to the EU/EEA the National Competent Authority for pharmaceutical products in the new Member State is considered equivalent to all other EU/EEA National Competent Authorities (NCA). This is based on the positive conclusion of the assessment carried out by the European Commission during the accession process (equivalence with the *acquis communautaire*) that also includes assessment of the capacity of the National Competent Authority to adequately implement the EU *acquis*.

To achieve and maintain equivalent supervision standards national Pharmaceutical Inspectorates have adopted a common quality system framework, as described in the Compilation of Union Procedures on Inspections and Exchange of Information, referred to in Article 3.1 of Directive 2017/1572 and recital (69) of Regulation 2019/6.

Equivalence is also achieved and maintained by harmonised implementation and interpretation of EU legislation and guidelines through the work of the Good Manufacturing and Distribution Practice Inspectors Working Group (GMDP IWG) and the implementation of Union Procedures by each Pharmaceutical inspectorate.

The Joint Audit Programme (JAP) forms an essential part of the quality system adopted by good manufacturing practice (GMP) inspectorates in the European Economic Area (EEA), aiming to ensure consistency of GMP compliance programmes and standards and a harmonised approach throughout EU/EEA.

Generally, the establishment and maintenance of common harmonised standards and procedures in the EU/EEA is achieved through:

- *Implementation of the Compilation of Union Procedures on Inspection and Exchange of Information (Community Procedures)*
- *Participation in the meetings of the Good Manufacturing and Distribution Practice Inspectors Working Group (GMDP IWG)*
- *Implementation of the Union guidelines for good manufacturing practice*
- *Participation in the meetings of the Heads of Medicines Agencies (HMA)*
- *Planning of appropriate and regular training of inspectors*
- *Participation in joint inspections with other EU/EEA inspectorates*
- *Participation in the audits of national competent authority inspectorates (Joint Audit Programme)*
- *Drafting Annual MRA maintenance reports (Annual Reports)*
- *Participation in the Benchmarking of Medicines Agencies (BEMA)*

In order to avoid duplication of effort and promote international harmonisation the EU/EEA maintenance programme should include similar or the same principles as other comparable maintenance programmes, e.g. those existing under MRAs or used by other organisations such as PIC/S. Also, participation in MRA and PIC/S audits using procedures harmonised with the EU/EEA is a useful training tool.

## 2. Purpose

The primary purpose of the maintenance programme is to safeguard adequate and equivalent standards applied in the supervision of the pharmaceutical companies in order to fulfil the obligations of the EU/EEA member states to

- protect public and animal health
- comply with the rules of the single market as laid down in the Treaty on the Functioning of the European Union and the EEA Agreement, and
- develop and maintain confidence and mutual trust between the EU/EEA national competent authorities as well as competent authorities outside the EU/EEA.

Further, the maintenance programme leads to the creation of a "Maintenance Dossier" (see under Section 6. Maintenance Dossier) for each EU/EEA Pharmaceutical inspectorate which will document its equivalence and contain or reference necessary evidence which can be supplied for information upon reasoned request from EU/EEA bodies (e.g. EC or HMA) and international partners (e.g. MRA partners, international organisations such as PIC/S, WHO and others where there are relevant international agreements in place).

Sharing of non-public information under the provisions of this programme is subject to the explicit consent of the concerned inspectorate and appropriate confidentiality agreements.

The Joint Audit Programme Compliance Group will exercise oversight in the operation of this maintenance programme and report to the GMDP IWG, the Heads of Medicines Agencies (HMA) and the European Commission.

## 6. Scope

This document outlines the elements needed for the establishment and maintenance of equivalence between EU/EEA Pharmaceutical GMP inspectorates, as regards their capability to exercise adequate supervision of the GMP compliance of pharmaceutical companies to protect public and animal health.

## 7. Definitions

In order to avoid duplication of definitions and a consequent introduction of inconsistencies only cross-references are provided.

4.1. Quality system: as defined in the Union Procedure "Quality Systems Framework for GMP Inspectorates"

4.2. Pharmaceutical Inspectorate: as defined in the Union Procedure "Quality Systems Framework for GMP Inspectorates"

4.3. *Acquis communautaire* - The *acquis* is the body of common rights and obligations that are binding on all EU countries, as EU Members. It is constantly evolving and comprises:

- the content, principles and political objectives of the Treaties;
- the legislation adopted in application of the treaties and the case law of the Court of Justice of the EU;
- the declarations and resolutions adopted by the EU;
- best practices applied by the EU inspectors' network
- measures relating to the common foreign and security policy;
- measures relating to justice and home affairs;



- international agreements concluded by the EU and those concluded by the EU countries between themselves in the field of the EU's activities.

Applicant countries have to accept the *acquis* and demonstrate that they have adequate administrative capacity to implement the *acquis* before they can join the EU. Derogations from the *acquis* are granted only in exceptional circumstances and are limited in scope and time. The *acquis* must be incorporated by applicant countries into their national legislation by the date of their accession to the EU as they are obliged to implement it from that date and be able to demonstrate the establishment of a sustainable and adequate Pharmaceutical Inspectorate / National Competent Authority.

(<http://eur-lex.europa.eu/summary/glossary/acquis.html>)

## 8. Components of the maintenance programme

The maintenance programme which relies on the Joint Audit Programme (JAP), is built on four pillars:

1. Inclusion in the maintenance programme
2. Periodic re-confirmation of equivalence
3. Periodic training on common standard
4. Exchange of information

### **5.1. Inclusion in the maintenance programme**

Following the positive conclusion of the EU accession process based on the assessment carried out by the European Commission (equivalence with the *acquis communautaire* and capacity to implement the *acquis*), the new Member States will be included in the maintenance and JAP programme (see JAP Procedure point 4.2. *Scope*).

The fulfilment of this condition includes the Pharmaceutical inspectorate in the EU/EEA Maintenance Programme.

### **5.2. Re-confirmation of equivalence**

The equivalence in supervision of the pharmaceutical industry should be re-confirmed at regular intervals in line with the JAP Procedure (see JAP Procedure point 4.2. *Scope*).

The Inspectorate should regularly participate in GMDP IWG meetings (at least 90% over 5 years) in order to contribute to harmonisation efforts and to maintain a common understanding and interpretation of GMP practices and requirements related to the supervision of the pharmaceutical industry, e.g. as laid down in the Compilation of Union Procedures and relevant EU legislation. In addition, active contribution to the Joint Audit Programme through provision of auditors is expected at least every two years.

### **5.3. Training on common standards**

The NCAs should foresee regular participation of the inspectors to trainings relevant to GMP inspections and GMP specific topics e.g., organised by EU health programmes, national or international bodies such as PIC/S or others.

In addition, contribution to a sustainable EU inspectors' network and a sustainable national Pharmaceutical Inspectorate should be aimed for through regular participation in joint third-country inspections with other EU/EEA authorities. Also, joint inspections with MRA partners, or participation in inspections resulting from PIC/S joint visits or EDQM programmes are possible and considered as supportive training activities. This will further strengthen the capacity of EU/EEA inspectors and JAP auditors to ensure compliance with GMP inspection capability and JAP audit procedures and will contribute to improvement of compliance with the EU pharma *acquis* and alignment with the EU pharma strategy to safeguard public and animal health. These joint inspections may concern centrally and nationally authorised products or active substances. The EMA will actively promote joint inspections as part of its GMP inspections programme while the EU/EEA pharmaceutical inspectorates shall cooperate with the Agency in line with Article 111 of Directive 2001/83/EC and with each other in line with Article 137 of

Regulation 2019/6 and are strongly encouraged to use the EudraGMDP planning module to identify suitable opportunities for joint inspections of third country sites.

#### **5.4. Exchange of information**

There should be evidence of active participation in exchange of information as described in the Compilation of Union Procedures including rapid alert notifications, EudraGMDP (e.g. GMP certificates, MIAs, non-compliance reports and inspection planning for third country inspections), product defects or other intelligence pertaining to risks related to the quality/safety/efficacy of medicinal products and active substances. This exchange of information is assessed during JAP audits.

## **9. Maintenance Dossier**

The Pharmaceutical inspectorate shall prepare and maintain a "Maintenance Dossier" covering the elements described under Section 5. Components of the maintenance programme.

It is for each pharmaceutical inspectorate to decide on the format and style of their maintenance dossier, but it must include, or make reference to, the quality system procedures and documents which define and evidence the activities and arrangements of the Inspectorate for maintaining its equivalence in supervision of the pharmaceutical industry. The maintenance dossier should be an integral part of the inspectorate's quality system established in line with the Compilation of Union Procedures.

The Maintenance Dossier should contain the following information (or reference to it in the quality system of the inspectorate):

#### **Maintenance Dossier Template for EU/EEA Pharmaceutical Inspectorates**

1. Initial EU pre-accession audit report (where available)
2. MRA Annual reports (at least since the last JAP audit and in line with national archiving policy)
3. Dates of internal audits
4. Audit reports by MRA partners, JAP, BEMA or other external audit programmes, including those of re-audits
5. Evidence of participation to trainings relevant to GMP inspections and any other relevant trainings on new technologies (reference to JAP audit report is sufficient)
6. Evidence of participation to joint inspections with other EU/EEA inspectorates and if applicable MRA, EDQM or PIC/S participating authorities
7. Evidence of participation to GMDP IWG meetings
8. Evidence of information sharing as described in the Compilation of Union Procedures (reference to JAP audit report is sufficient)
9. Evidence of regular data entry into the EudraGMDP (certificates, authorisations, non-compliance reports and inspection plans) (reference to JAP audit report is sufficient)
10. Other related factors (e.g., presence of trained JAP auditors or relevant items arising from BEMA and HMA meetings)
11. Evidence of sustainability of the NCA, i.e. capacity to ensure compliance with GMP inspections procedures and frequency and JAP audit requirements (reference to JAP audit report and if applicable cooperation agreements with other NCAs is sufficient).

The contents of the Maintenance Dossier are subject to the archiving policy of the pharmaceutical inspectorate.

## 10. Oversight

Senior management of the National Competent Authority, of which the Pharmaceutical inspectorate is part, shall make a formal commitment to the recommended principles embodied in this document by ensuring that the maintenance programme of the Inspectorate is documented and that it is implemented.

The implementation and maintenance of the dossier described under paragraph 6 is within the responsibility of the nominated person(s) responsible for carrying out the quality assurance function as referred to in the Union Procedure „Quality systems framework for GMP inspectorates“, point 7.3.

The Joint Audit Programme Compliance Group will exercise Union level oversight over the adherence to the elements of the maintenance programme by the EU/EEA Pharmaceutical inspectorates through regular JAP audits and MRA annual reports.

The JAP Compliance Group will also provide assessment of the equivalence status of a Pharmaceutical Inspectorate if requested by the HMA, GMDP IWG, or the European Commission. Such assessment will be based on the audit history of the Pharmaceutical Inspectorate.

## 11. Financing

All expenses incurred in connection with the maintenance programme have to be borne by the EU/EEA Member States individually, unless there is a specific budget made available notably through the European Commission's Health Programmes.

## **Part II - interpretation documents and templates**

# Interpretation of the Union format for Manufacturer/Importer Authorisation

## Table of contents:

1. Introduction
2. Union format for manufacturer's authorisation

<b>Title</b>	<b>Interpretation of the Union Format for Manufacturer/Importer Authorisation</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Interpretation of the Union format for Manufacturer/Importer Authorisation

## 1. Introduction

The purpose of this document is to provide guidance to industry and regulators on the interpretation of activities defined on Manufacturer's / Importer's Authorisation (MIA) issued by Competent Authorities in the EEA. The text from the 'Union Format for a Manufacturer's Authorisation' is reproduced below and where necessary, clarifying guidance text is provided under certain MIA entries in shaded text boxes. The guidance in these text boxes applies to human and veterinary medicinal products (Annex 1) and also to Investigational Medicinal Products (Annex 2). The headings in Annex 2 are not included in this document but any specific guidance which applies to IMPs only is identified where necessary. Clarifying remarks are often important in helping to define the scope of an MIA. When necessary and wherever possible these should be cross referenced to the number items within the MIA.

## 2. Union Format for manufacturer/importer<sup>1</sup> authorisation

1. Authorisation number

2. Name of authorisation holder

2.a Alternative name of authorisation holder (optional)

3. Address(es) of manufacturing site(s)

(All authorised sites should be listed if not covered by separate licences)

3.a Additional details on units inspected of manufacturing site(s) address(es) (optional)

4. Legally registered address of authorisation holder

4.a Additional details on units inspected of legally registered address (optional)

Appropriate documentation should be provided by the manufacturer/importer to the relevant Competent Authority as evidence of the name of the Authorisation Holder legally registered address. This address may differ from the address where manufacturing activities take place.

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<sup>1</sup> The authorisation referred to in paragraph 40(1) of Directive 2001/83/EC as amended and Article 88(1) of Regulation (EU) 2019/6, shall also be required for imports coming from third countries into a Member State.

Guidance on the interpretation of this template can be found in the Interpretation of the Union format for Manufacturer/Importer Authorisation

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 Annex2

Annex 1 describes manufacturing / importation operations relating to Human or Veterinary medicines.

Annex 2 describes manufacturing / importation operations relating to Investigational Medicinal Products (IMPs)

There are optional Annexes which may be used to various different extents by EEA Competent Authorities. The Annexes which are relevant to the MIA issued by the CA should be listed in this section.

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)<sup>1</sup>

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<sup>1</sup>The Competent Authority is responsible for the appropriate linking of the authorisation with the manufacturer's application (Article 42(3) of Directive 2001/83/EC as amended and Article 90(3) of Regulation (EU) 2019/6).

Name and address of the site:

If an MIA includes a number of addresses, then, a separate Annex 1 should be completed in relation to the specific manufacturing operations carried out at each site address.

- 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**

The scope of manufacturing operations which are authorised at the site is defined using the following unit operations. Each of the following individual operations carried out by the Authorisation holder should be identified on the MIA, as appropriate.

- \*Processing Operations:** this includes any or all processing steps in the manufacture of a dosage form.
- \*Primary Packing:** this refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product.
- Secondary Packing:** this refers to placing the medicinal product, which is already sealed within its primary packaging material within an outer packaging material. This also includes labelling operations or the assembly of other components which are specified in the Marketing Authorisation (or Product Specification File in the case of an IMP) to form the finished product pack.
- Batch Certification:** this refers to the certification of a finished product batch of medicinal product by a Qualified Person before its release into the marketplace or before a batch is exported. For an IMP, this refers to the QP certification of the batch of IMP before release to the clinical trial sponsor or before export.
- Quality Control:** refers to types of laboratory testing which the MIA holder is authorised to perform.

\* Using the guidance described in Chapters 3 and 5 of the GMP Guide, manufacturers should evaluate materials which are handled at the site with regard to the risk posed in terms of their potency, toxicity or potential for sensitisation. If a site is authorised to carry out processing



operations or primary packing activities on substances or products which are considered to be highly sensitising, highly potent or highly toxic or have a specific hazard (e.g. radiopharmaceuticals) then this should be identified in relation to the particular dosage form using the relevant items from the drop down list on EudraGMDP.

Any restrictions (e.g. if product is to be manufactured in a dedicated facility) which may apply in relation to these products should be included in the clarifying remarks with reference to the relevant dosage form.

#### Drop Down Menu Items from EudraGMDP

- $\beta$ -Lactam antibiotics
- Other highly sensitising materials
- Live cells
- Pathogenic Organisms (Biosafety 3 or 4)
- Radiopharmaceuticals
- Ectoparasitocides
- Others (Free text entry)

Examples of products to be included under 'Other' category include

- Highly potent products
- Highly toxic products

Storage: Any site which holds an MIA and carries out processing operations or packaging of medicinal products is also understood to be authorised for storage. If a site is carrying out other manufacturing operations where storage is not automatically understood to be included, as described above, then section 1.4.3 <Other> should be used to identify storage activity

#### Distribution

Any site which holds an MIA and which carries out manufacturing operations on batches of medicinal products is also authorised to distribute those batches of medicinal products unless there is a comment to the contrary in the clarifying remarks

#### Real Time Release Testing

If a manufacturer is authorised to carry out real time release testing instead of one or more finished product tests then this should be identified as a clarifying remark in relation to the processing operations for the particular dosage form. The type of real time release testing which is authorised should also be identified in the clarifying remark. The use of Real Time Release testing should reflect any relevant requirements described in a Marketing Authorisation or Clinical Trial Application.

Note: where a category is selected which includes a provision for <free text> then relevant descriptive text must be entered in the <free text> box.

## 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 <free text>

Examples of activities to be captured under 1.1.1.6 'Other'

'Manufacture of sterile active substance' - (where this activity is normally authorised as a finished product manufacturing activity by the Competent Authority issuing the MIA).

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

Where terminal sterilisation of a product is not carried out on site by the MIA holder but is contracted out to another site, a comment such as 'terminal sterilisation by gamma irradiation is outsourced to another site' should be entered in relation to that dosage form in the clarifying remarks section.

- 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 <free text>

### 1.1.3 Batch certification

This is understood to apply to all sterile dosage forms unless restrictions are stated in the clarifying remarks.

## 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 <free text>

1.2.1.9 'Pressurised preparations' are defined as preparations presented in special containers under pressure of a gas. If, for example, a liquid aerosol is generated by mechanical pumping action rather than a propellant then such dosage forms would be categorised as 'Liquids for external use' or 'Liquids for internal use', as appropriate.

Examples of activities to be captured under 1.2.1.17 'Other'

'Manufacture of intermediates' (these should be specified e.g. powders for further processing)

'Overencapsulation' (this activity is usually applicable to IMPs and controls may differ from those used in filling a standard hard shell capsule product)

### 1.2.2 Batch certification

This is understood to apply to all non-sterile dosage forms unless restrictions are stated in the clarifying remarks.

## 1.3 Biological medicinal products

### **Definition of a Biological Medicinal Product / Biological substance**

**Biological medicinal product:** is a medicinal product, the active substance of which is a biological substance.

**Biological substance:** is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

#### *1.3.1 Biological Medicinal Products (List of product types)*

### **Categorisation of Biological Products**

The following product categories should be used to identify if a site is carrying out any processing steps relating to the manufacture of a biological product. The manufacture of the biological substance may be part of the continuum of processing steps in the manufacture of the finished biological product and these operations should also be captured under this section, where appropriate. Where the authorised operations also include manufacture of the finished dosage form for the biological product then the relevant dosage form should also be selected on the MIA (e.g. 1.1.1.2 Lyophilisates).

#### Blood products

This category should be selected where there are processing operations performed in relation to biological products containing an active substance isolated from blood. Examples of such products include albumin, plasma Factor VIII or Immunoglobulins which are isolated from blood. The processing of Factor VIII which is manufactured using a biotechnology method would not be included in this category. For a human medicine, the steps in the manufacture of a blood product which come under an MIA are those processing steps which are not covered under Directive 2002/98/EC.

#### Immunological products

This category should be selected where there are processing operations carried out in relation to manufacture of biological products which have an immunological mode of action (e.g. vaccines).

#### Cell therapy products

This category should be selected where there are processing operations carried out in relation to the manufacture of cell therapy products. The steps in the manufacture of cell therapy product which come under an MIA are those steps which are not covered under Directive 2004/23/EC.

#### Gene therapy products

This category should be selected where there are processing operations carried out in relation to the manufacture of gene therapy products. The steps in the manufacture of a gene therapy product which come under an MIA are those steps which are not covered under Directive 2004/23/EC.

#### Biotechnology products

Biotechnology includes the use of genetically modified mammalian cells or micro-organisms, (e.g. bacteria or yeasts), or biological substances (e.g. enzymes), in the manufacture a biological products. This category should be selected where there are processing operations carried out in relation to the manufacture of biological products using biotechnology.

#### Human or animal extracted products

This category should be selected where processing steps are carried out in relation to the manufacture of a biological product containing active substances derived from human or animal sources (cells, tissues, fluids), with the exception of blood.

#### Tissue engineered products

This category should be selected where processing steps are carried out in relation to the manufacture of tissue engineered products.

#### Other products (specify)

This category should be selected where processing steps are carried out in relation to manufacture of a biological product which includes a biological active substance which does not fit into the previously

This category should be selected where processing steps are carried out in relation to manufacture of a biological product which includes a biological active substance which does not fit into the previously named categories.

- 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 <free text>

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

This section should be completed with regard to final QP certification of the finished dosage form of a biological product. Entries should also be made under 1.1.3 or 1.2.2, as appropriate, to reflect the type of dosage form being certified.

- 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 <free text>

#### **1.4 Other products or manufacturing activity**

Note: where a manufacturer carries out processing steps in relation to herbal or homoeopathic dosage forms (e.g. tablets) then there should be an entry for the relevant dosage form (sections 1.1 to 1.2) in addition to the entry in the section below. Where the facility is only authorised for manufacturing operations in relation to herbal or homoeopathic products then a clarifying remark ('herbal products only' or 'homoeopathic products only') should be included in relation to the dosage forms / manufacturing operation authorised on the MIA.

#### 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

This section is intended to be completed where these sterilisation activities are not carried out as part of the manufacture of a dosage form, for example, where the MIA holder is a contract sterilisation facility performing gamma irradiation of products on behalf of other manufacturers.

- 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>

#### Examples of activities to be listed under 1.4.3

'Storage' – (for example 'storage' would be included here where a site only carries out batch certification and storage of medicinal products)

### 1.5 Packaging

#### 1.5.1 Primary packing

Primary packing of a sterile product is taken as being included as part of the processing operations covered under section 1.1 in relation to sterile products unless a comment to the contrary is entered in the clarifying remarks in relation to the particular dosage form.

- 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 <free text>

Examples of activities to be captured under 1.5.1.17 'Other'

If the MIA holder carries out primary packing but not the actual manufacture of a dosage form (e.g. implants) which subsequently undergoes terminal sterilization, a statement as below should be entered under 'Other' 1.5.1.17.

'Primary packing of (*name of dosage form*) which undergoes terminal sterilisation'

1.5.2  Secondary packing

Where secondary packaging is authorised it is understood to apply to all dosage forms unless otherwise specified in the clarifying remarks.

**1.6 Quality control testing**

Where Quality Control testing is carried out at the site then authorised categories of testing should be identified below.

- 1.6.1  Microbiological: sterility
- 1.6.2  Microbiological: non-sterility
- 1.6.3  Chemical/Physical
- 1.6.4  Biological

Test Categories	Category obligatory for these tests
<b>Microbiology Sterility</b>	Sterility Test
<b>Microbiology Non Sterility</b>	Testing involving culturing, enumeration and identification of micro-organisms, Preservative efficacy testing
<b>Chemical / Physical Testing</b>	Testing of quality attributes by physical or chemical means e.g. Physical measurements Wet Chemistry Chromatographic techniques
<b>Biological Testing</b>	Tests involving use of live cultured animal cells or animals and tests utilising materials of biological origin (e.g. antibodies, antigens). Examples of such tests would include, Rabbit Pyrogen, ELISA, Monocyte Activation Test & qPCR Endotoxin testing (e.g. gel clot, turbidometric or chromogenic methods.)

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



Unless a clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing on the MIA format, should be included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone.

## Part 2 - IMPORTATION OF MEDICINAL PRODUCTS

### 2.1 Quality control testing of imported medicinal products

Where Quality Control testing is carried out at the site in relation to imported medicinal products, the authorised categories of testing should be identified below. This section should be completed, where applicable, even if entries have been made under section 1.6.

- 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

This section should be completed where the site performs certification of either an imported finished product or a bulk dosage form which undergoes packing after importation. If the MIA holder is also the site of physical importation then an entry should also be made under 2.3.1.

For **IMP** manufacturers (Annex 2), authorisation to carry out certification of imported **comparator** products should be identified by a clarifying remark in relation to the relevant product category below.

- 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*

The relevant dosage form under 2.2.1 or 2.2.2 should also be identified above in addition to the category of biological product below.

- 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 <free text>

### 2.3 Other importation activities (any other relevant importation activity that is not covered above)

- 2.3.1  *Site of physical importation*

An entry here means that the site is authorised to receive and store imported product which is awaiting QP certification. Certification must be identified separately in relation to the relevant product categories under section 2.2.

2.3.2  *Importation of intermediate which undergoes further processing*

The type of intermediate should be specified e.g. granulate, sterile active substance, partially manufactured biological product. This point covers not only finished product intermediate but also bulk products

2.3.3  *Biological active substance*

2.3.4  *Other <free text>*

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

Unless a clarifying remark is intended as a general comment relating to activities at the site, a numerical reference a, as per the item listing on the MIA format, should be included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone.

**ANNEX 3 (Optional)**

Address(es) of Contract Manufacturing Sites

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

**ANNEX 4 (Optional)**

Address(es) of Contract Laboratories

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

**ANNEX 5 (Optional)**

Name(s) of Qualified Person(s)

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

**ANNEX 6 (Optional)**

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

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

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

.....  
.....

.....

**ANNEX 7 (Optional)**

Date of Inspection on which authorisation was granted                      dd / mm / yyyy

Scope of last Inspection

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

**ANNEX 8 (Optional)**

Products authorised to be manufactured/imported (in accordance with Articles 41 and 42 of Directive 2001/83/EC, as amended or Articles 89 and 90 of Regulation (EU) 2019/6).

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# Interpretation of the Union format for GMP certificate

## Table of contents:

1. Introduction
2. Union format for GMP certificate

<b>Title</b>	<b>Interpretation of the Union format for GMP certificate</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Interpretation of the Union format for GMP certificate

## 1. Introduction

The purpose of this document is to provide guidance to industry and regulators on the interpretation of activities defined on GMP certificates issued by Competent Authorities in the EEA. Where necessary, clarifying guidance text is provided under certain GMP certificate entries in shaded text boxes. The guidance in these text boxes applies to human medicinal products, veterinary medicinal products and Investigational Medicinal Products (IMPs). Any specific guidance which applies to IMPs only is identified where necessary. Whilst there is no European legal requirement for the authorisation of active substance manufacturers, GMP certificates may be issued following inspection of these sites either within the EEA or in third countries. Details for GMP certification of active substance manufacturers are included in sections 3 & 4 of this document.

Guidance is provided in certain other EudraGMDP Q&As in relation to information to be provided in Part 1 of the EU format for a GMP certificate and no further guidance is provided in relation to Part 1 in this document. The following guidance relates to Part 2 only.

### 1. MANUFACTURING OPERATIONS – MEDICINAL PRODUCTS

The scope of manufacturing operations which are certified at the site is defined using the following unit operations. Each of the following individual operations carried out at the certified site should be identified as appropriate.

\*Processing Operations: this includes any or all processing steps in the manufacture of a dosage form.

\*Primary Packaging: this refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product, i.e. immediate packaging.

Secondary Packaging: this refers to placing the medicinal product, which is already sealed within its primary packaging material within an outer packaging material, i.e. outer packaging. This also includes labelling operations or the assembly of other components which are specified in the Marketing Authorisation (or Product Specification File in the case of an IMP) to form the finished product pack.

Batch Certification: this refers to the certification of a finished product batch of medicinal product by a Qualified Person at an authorised manufacturing site in the EEA before its release into the market place or before a batch is exported. For an IMP, this refers to the QP certification of the batch of IMP at an authorised manufacturing site before its release to the clinical trial sponsor or before export.

Quality Control: refers to types of laboratory testing for which the site is certified.

\*Using the guidance described in Chapters 3 and 5 of the EU GMP Guidelines, Volume 4 of the EudraLex, Part I, manufacturers should evaluate materials which are handled at the site with regard to the risk posed in terms of their potency, toxicity or potential for sensitisation. If a site is considered GMP certified with regard to processing operations or primary packing activities on substances or products which are considered to be highly sensitising, highly potent or highly toxic or have a specific hazard (e.g. radiopharmaceuticals), then this should be identified in relation to the particular dosage form using the relevant items from the drop down list on EudraGMDP. Any restrictions (e.g. if the product is to be manufactured in a dedicated facility) which may apply in relation to these products should be included in the clarifying remarks with reference to the relevant dosage form.

#### Drop Down Menu Items from EudraGMDP

- $\beta$ -Lactam antibiotics
- Other highly sensitising materials
- Live cells
- Pathogenic Organisms (Biosafety 3 or 4)
- Radiopharmaceuticals
- Ectoparasiticides
- Others (Free text entry)

Examples of products to be included under 'Other' category include

- Highly potent products
- Highly toxic products

Storage: Any site which carries out processing operations or packaging of medicinal products is also understood to be GMP certified for storage. If a site is carrying out other manufacturing operations where storage is not automatically understood to be included, as described above, then section 1.4.3 <Other> should be used to identify storage activity.

#### Distribution

Any site which holds a Manufacturers / Importers Authorisation (MIA) in the EEA and carries out manufacturing operations on batches of medicinal products is also authorised to distribute those batches of medicinal products unless there is a comment to the contrary in the clarifying remarks. Such sites are also considered GDP certified in relation to these activities unless there is a comment to the contrary within the clarifying remarks.

#### Real Time Release Testing

If a manufacturer is considered GMP certified in relation to the performance of real time release testing instead of one or more finished product tests then this should be identified as a clarifying remark in relation to the processing operations for the particular dosage form. The type of real time release testing which is certified should also be identified in the clarifying remark. The use of Real Time Release testing should reflect any relevant requirements described in a Marketing Authorisation or Clinical Trial Application.



Note: where a category is selected which includes a provision for <free text> then relevant descriptive text must be entered in the <free text> box.

## 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 <free text>

#### Examples of activities to be captured under 1.1.1.6 'Other'

'Manufacture of sterile active substance', where this activity is normally authorised as a finished product manufacturing activity by the Competent Authority which is issuing the GMP certificate.

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

Where terminal sterilisation of a product is not carried out on site by the certified site but is contracted out to another site, a comment such as "terminal sterilisation by gamma irradiation is outsourced to another site" should be entered in relation to that dosage form in the clarifying remarks section.

- 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 <free text>

### 1.1.3 Batch certification

This is understood to apply to all sterile dosage forms unless restrictions are stated in the Clarifying Remarks.

## 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 <free text>

1.2.1.9 'Pressurised preparations' are defined as preparations presented in special containers under pressure of a gas. If, for example, a liquid aerosol is generated by mechanical pumping action rather than a propellant then such dosage forms would be categorised as 'Liquids for external use' or 'Liquids for internal use', as appropriate.

Examples of activities to be captured under 1.2.1.17 'Other'

'Manufacture of intermediates' (*these should be specified e.g. powders for further processing*)

'Over-encapsulation' (*this activity is usually applicable to IMPs and controls may differ from those used in filling a standard hard shell capsule product*).

1.2.2  Batch certification

This is understood to apply to all non-sterile dosage forms unless restrictions are stated in the Clarifying Remarks.

### 1.3 Biological medicinal products

#### **Definition of a Biological Medicinal Product / Biological substance**

**Biological medicinal product:** is a medicinal product, the active substance of which is a biological substance.

**Biological substance:** is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

### 1.3.1 Biological Medicinal Products (List of product types)

#### **Categorisation of Biological Products**

The following product categories should be used to identify if a site is carrying out any processing steps relating to the manufacture of a biological product. The manufacture of the biological substance may be part of the continuum of processing steps in the manufacture of the finished biological product and these operations should also be captured under this section, where appropriate. If the certifying authority does not consider the processing steps to be partial manufacture of a biological medicinal product then the activities should be recorded, as appropriate, in sections 3 & 4 of the GMP certificate which relate to manufacturing operations for active substances.

Where the certified operations also include manufacture of the finished dosage form for the biological product then the relevant dosage form should also be selected on the GMP certificate (e.g. 1.1.1.2 Lyophilisates).

#### **Blood products**

This category should be selected where there are processing operations performed in relation to biological products containing an active substance isolated from blood. Examples of such products include albumin, plasma Factor VIII or Immunoglobulins which are isolated from blood. The processing of Factor VIII which is manufactured using a biotechnology method would not be included in this category. For a human medicine, the steps in the manufacture of a blood product which come under a GMP certificate are those processing steps which are not covered under Directive 2002/98/EC.

#### **Immunological products**

This category should be selected where there are processing operations carried out in relation to manufacture of biological products which have an immunological mode of action (e.g. vaccines, allergens).

#### **Cell therapy products**

This category should be selected where there are processing operations carried out in relation to the manufacture of cell therapy products. The steps in the manufacture of cell therapy product which come under a GMP certificate are those steps which are not covered under Directive 2004/23/EC.

#### **Gene therapy products**

This category should be selected where there are processing operations carried out in relation to the manufacture of gene therapy products. The steps in the manufacture of a gene therapy product which come under a GMP certificate are those steps which are not covered under Directive 2004/23/EC.

### Biotechnology products

Biotechnology includes the use of genetically modified mammalian cells or micro-organisms, (e.g. bacteria or yeasts), or biological substances (e.g. enzymes), in the manufacture a biological products. This category should be selected where there are processing operations carried out in relation to the manufacture of biological products using biotechnology.

### Human or animal extracted products

This category should be selected where processing steps are carried out in relation to the manufacture of a biological product containing active substances derived from human or animal sources (cells, tissues, fluids), with the exception of human blood, cells or tissues in which case the products may be more be more appropriately categorised as "Blood products", "Cell therapy products" or "Tissue engineered products".

### Tissue engineered products

This category should be selected where processing steps are carried out in relation to the manufacture of tissue engineered products.

### Other products (specify)

This category should be selected where processing steps are carried out in relation to manufacture of a biological product which includes a biological active substance which does not fit into the previously named categories.

- 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 <free text>

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

This section should be completed with regard to QP certification of the finished dosage form of a biological product. Entries should also be made under 1.1.3 or 1.2.2, as appropriate, to reflect the type of dosage form being certified.

- 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 <free text>

## **1.4 Other products or manufacturing activity**

Note: where a manufacturer carries out processing steps in relation to manufacture of herbal or homoeopathic dosage form (e.g. tablets) then there should be an entry for the relevant dosage form (sections 1.1 to 1.2) in addition to the entry in the section below. Where the facility is only certified for manufacture of herbal or homoeopathic products then a clarifying remark (herbal products only or homoeopathic products only) should be included in relation to the dosage forms.

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*

This section is intended to be completed where these sterilisation activities are not carried out as part of the manufacture of a dosage form, for example where the certificate holder is a contract sterilisation facility performing gamma irradiation of products on behalf of other manufacturers.

- 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>*

Examples of activities to be listed under 1.4.3

*'Storage'*

*For example 'storage' would be included here where a site only carries out batch certification and storage of medicinal products. Storage of stability samples could also be listed here where this is the specific activity which is being carried out at the certified site.*

*'Manufacture of Excipient Material'*

*The name of the excipient material covered within the scope of the GMP certificate should be also be specified. Include summary detail on the nature of the excipient and the type of manufacturing operations being certified within the clarifying remarks section.*

## 1.5 Packaging

### 1.5.1 Primary packaging

Primary packing of a sterile product is taken as being included as part of the processing operations covered under section 1.1 unless a comment to the contrary is entered in the clarifying remarks in relation to the particular dosage form.

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

#### Examples of activities to be captured under 1.5.1.17 'Other'

If the certified site carries out primary packing but not the actual manufacture of a dosage form (e.g. implants) which subsequently undergoes terminal sterilization, a statement as below should be entered under 'Other' 1.5.1.17.

'Primary packing of (*name of dosage form*) which undergoes terminal sterilisation'

### 1.5.2 Secondary packaging

Where secondary packaging is certified it is understood to apply to all dosage forms unless otherwise specified in the clarifying remarks.

## 1.6 Quality control testing

The Quality Control testing covered within the scope of the GMP Certificate should be identified using categories described below.

- 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**

Unless a clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing on the GMP certificate format, should be included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone.

Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.

## 2. IMPORTATION OF MEDICINAL PRODUCTS

### 2.1 Quality control testing of imported medicinal products

Where Quality Control testing is carried out at the site located in the EEA in relation to imported medicinal products, the certified categories of testing should be identified below. This section should be completed, where applicable, even if entries have been made under section 1.6.

- 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

This section should be completed where the certified operations at a site located in the EEA includes batch certification of either an imported finished product or a bulk dosage form which undergoes packing after importation. If the certified site is also the site of physical importation then an entry should also be made under 2.3.1.

For **IMP** manufacturers (Annex 2), batch certification of imported **comparator** products should be identified by a clarifying remark in relation to the relevant product category below.

#### 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.

The relevant dosage form under 2.2.1 or 2.2.2 should be identified above in addition to the category of biological product below.

- 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 <free text>



## 2.3 Other importation activities (any other relevant importation activity that is not covered above)

### 2.3.1 Site of physical importation

An entry here means that the site is certified for receipt and storage of imported product which is awaiting QP certification. QP certification must be identified separately in relation to the relevant product categories under section 2.2.

### 2.3.2 Importation of intermediate which undergoes further processing

The type of intermediate should be specified e.g. granulate, sterile active substance, partially manufactured biological product. This point covers not only finished product intermediate but also bulk products.

### 2.3.3 Biological active substance

### 2.3.4 Other <free text>

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

Unless the clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing in the GMP certificate format, should be included wherever a clarifying remark or restriction is applied.

Clarifying remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone. Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.

### 3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:

The names of the active substance manufactured at the site should be entered above and the applicable manufacturing operations which are being certified in relation to that active substance should be identified in Sections 3.1 – 3.5 below. This should be repeated for each active substance manufactured at the site. If the site manufactures an active substance intermediate then the text “active substance intermediate(s)” should be entered above and the relevant manufacturing operations identified as described previously. The name of the active substance intermediate(s) should be entered as a clarifying remark.

#### Real-Time Release Testing

Where an active substance manufacturer is considered GMP certified in relation to performance of real time release testing instead of one or more quality control tests then this should be identified as a clarifying remark in relation to the relevant active substance. The type of real time release testing which is authorised should also be identified in the clarifying remarks.

3.1.1 includes any steps from manufacture of the defined starting materials until the step prior to manufacture of the crude active substance

- 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>

Items 3.2.1, 3.2.2 and 3.2.3 are completed below where the activities are not considered by the certifying authority to be partial manufacture of a medicinal product and therefore not covered under section 1.3 of the GMP certificate. Item 3.2.5 relates to either physical or chemical modification of the extracted active substance. Activities such as drying or milling are captured under the section on general finishing steps (3.5).

The term “extraction” used in the title of this section is a general term to cover a number of methods by which an active substance can be isolated from a natural source. The following are some examples:

- extraction of a herbal substance from plants should be entered under 3.2.1.
- purification of a herbal extract by distillation or fractionation should be entered under 3.2.6 and a reference to the plant source from which the extract has been obtained should be included (3.2.1.).
- manufacture of an active substance gas by an air separation process should be entered under 3.2.7.

- 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

This section is completed where the manufacturing activities in relation to a biological active substance are not considered to be covered under section 1.3 of the GMP certificate.

- 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)

This section is completed in relation to certification of those steps in the manufacturing process which render an active substance sterile. If a Competent Authority considers the steps which render an active substance sterile as partial manufacture of the medicinal product then relevant entries should also be made under Section 1.1. of the GMP certificate.

- 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

This section should be completed in relation to quality control testing of active substances or intermediates which are manufactured at the site. This section should be completed even if entries have been made under sections 1.6 and 2.1 relating to medicinal products manufactured at the same site.

A site which is GMP certified under 3.6.3 is also considered GMP certified in relation to microbiological testing activities other than sterility testing (i.e. activities under 3.6.2) unless a comment to the contrary is included in the restrictions /clarifying remarks section.

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

This section should be completed in relation to activities which are not described above. A description of the activity should be entered below.

<free text>

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

Unless the clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing in the GMP certificate format, should be included wherever a clarifying remark or restriction is applied. Where remarks apply to a particular active substance then the name of the active substance should be listed in the remark in addition to the numerical reference for the relevant activities.

Clarifying remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone. Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.

# Interpretation of the Union format for a wholesale distribution authorisation (medicinal products for human use)

## 3. Table of contents

1. Union format for a wholesale distribution authorisation (medicinal products for human use)

<b>Title</b>	<b>Interpretation of the Union format for a wholesale distribution authorisation (medicinal products for human use)</b>
Date of adoption	21 September 2021
Date of entry into force	9 months after publication
Supersedes	
Reason for revision	
Notes	<i>To be updated with the next revision</i>

# Interpretation of the Union format for a wholesale distribution authorisation (medicinal products for human use)

## Union format for a wholesale distribution authorisation (medicinal products for human use)

SCOPE OF WHOLESALE DISTRIBUTION AUTHORISATION	
1. MEDICINAL PRODUCTS	Examples of use
1.1. with a Marketing Authorisation in EEA country(s)	<p>WDA holder can perform the authorised operations on any medicinal products for human use, which have a marketing authorisation in any country of the European Union and in Iceland, Norway and Lichtenstein (EEA).</p> <p>It is not required that the medicinal product is authorised in the country of the WDA holder if the product is not going to be distributed to persons authorised or entitled to supply to the public in that country or the notification included in Art 76 of 2001/83/EC is applied.</p>
1.2. without a Marketing Authorisation in the EEA and intended for EEA market <sup>1</sup>	<p>This paragraph should be ticked when a WDA holder performs the following wholesaling activities:</p> <p>For example</p> <ul style="list-style-type: none"> <li>• Medicinal products for use as referred to in Art 5 of Directive 2001/83/EC or Art 83 of Regulation EC/726/2004.</li> <li>• Investigational Medicinal Products (IMPs) when a WDA is required by national legislation for the distribution of IMPs.</li> </ul>
1.3. without a Marketing Authorisation in the EEA and intended for exportation	<ul style="list-style-type: none"> <li>• Medicinal products referred to in Art 85a of Directive 2001/83/EC, which are directly received from a third country and exported to third countries without being imported into the EEA.</li> <li>• Medicinal products manufactured in the EEA, but intended for exportation outside the EEA only.</li> </ul>

<sup>1</sup> Art 5 of Directive 2001/83/EC or Art 83 of Regulation EC/726/2004

## SCOPE OF WHOLESALE DISTRIBUTION AUTHORISATION

2. AUTHORISED WHOLESALE DISTRIBUTION OPERATIONS	Examples of operations
2.1. Procurement	Obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors.
2.2. Holding	<p>Storing medicinal products.</p> <p>Holding means being in physical possession of the medicinal products, without necessarily owning them.</p> <p>Contract warehouses which are actually doing the storing and handling of medicinal products for another WDA holder.</p> <p>A transporter may require a WDA, if they are storing medicinal products for unjustified periods of time during their chosen route of transportation.</p> <p>Custom bonded warehouses: consolidation of freight, storage within free ports (inland container storage sites).</p>
2.3. Supply	All activities of providing / selling / donating medicinal products to wholesalers; pharmacies; or persons authorised or entitled to supply medicinal products to the public.
2.4. Export	All activities relating to the export procedure as defined in the GDP guidelines (i.e. allow Union goods to leave the customs territory of the Union. For the purpose of the guidelines, the supply of medicines from EU Member State to a contracting State of the European Economic Area is not considered as export).
2.5. Other activities(s): (please specify)	Member States may add other activities for which an authorisation is required according to national legislation (e.g. parallel distribution, parallel importation, products received back during recalls, returned IMPs...).
3. MEDICINAL PRODUCTS WITH ADDITIONAL REQUIREMENTS	
3.1. Medicinal products according to Art. 83 of Directive 2001/83/EC	<p>Additional requirements may be laid down by the member state in respect of wholesale distribution for the following categories of medicinal products.</p> <p>The competent authority may decide not to make available to the public details of these activities.</p>

## SCOPE OF WHOLESALE DISTRIBUTION AUTHORISATION

<b>3.1.1.</b> Narcotic or psychotropic products	
<b>3.1.2.</b> Medicinal products derived from blood	
<b>3.1.3.</b> Immunological medicinal products	Vaccines fall under this category
<b>3.1.4.</b> Radiopharmaceuticals (including radionuclide kits)	
<b>3.2.</b> Medicinal gases	
<b>3.3.</b> Cold chain products (requiring low temperature handling)	Refer to labelling information
<b>3.4.</b> Other products: (please specify here or make a reference to Annex 5)	Member States may use this section to reflect national requirements
<b>Any restrictions or clarifying remarks related to the scope of these wholesaling operations</b>	All restrictions, such as for a certain category of products only, or certain activities, should be written here.
<b>Optional Annexes</b>	
<b>Annex 2</b>	Only outsourced wholesale distribution operations should be listed here.
<b>Annex 3</b>	Annex 3 is used to list the name of the Responsible Person (s) used by the WDA holder.
<b>Annex 4</b>	Annex 4 is used to give the date of the inspection on which the WDA was granted.
<b>Annex 5</b>	Annex 5 is used to list any other additional provisions in accordance with national legislation.



## GMP inspection report – Union format

### Table of contents:

1. GMP inspection report - Union format
2. Definition of significant deficiencies

<b>Title</b>	<b>GMP inspection report - Union format</b>
Date of adoption	31 January 2010
Date of entry into force	1 August 2010
Supersedes	Version in force from October 2005
Reason for revision	The format was aligned with activities and amendments made in order to enable summary reports for European Medicines Agency inspections to be discontinued
Notes	Not applicable

# GMP inspection report - Union format<sup>1</sup>

<b>Report Reference no.:</b>			
<b>Name of product(s) and pharmaceutical form(s):</b>			
<i>Essential for inspections requested by the European Medicines Agency otherwise only necessary for product specific inspections.</i>			
<b>Inspected site(s):</b>			
<i>Name and full address of the inspected site, including exact location/designation of the production facilities inspected.</i>			
<i>EudraGMDP reference number</i>			
<i>Site location identifier (DUNS number/GPS coordinates)</i>			
<b>Activities carried out:</b>			
	<i>Human</i>	<i>Veterinary</i>	<i>IMP</i>
<i>Manufacture of finished products</i>			
<i>Sterile</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Non-sterile</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Biologicals</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Sterilisation of excipient, active substance or medicinal product</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Primary packaging</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Secondary packaging</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Quality control testing</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Importing</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Batch certification</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Storage and distribution</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Manufacture of active substance</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Other _____</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Inspection date(s):</b>	<i>Date(s), month, year.</i>		
<b>Inspector(s) and Expert(s):</b>			
<i>Name(s) of the inspector(s).</i>			
<i>Name(s) of expert / assessor (if applicable).</i>			
<i>Name(s) of the Competent Authority(ies).</i>			
<b>References:</b>	<i>Reference number of marketing and / or manufacturing authorisations.</i>		
	<i>EMA reference number(s) if the inspection is requested by the European Medicines Agency.</i>		
<b>Introduction:</b>			

<sup>1</sup> The Union format for a GMP inspection report has been established in accordance with Art. 111a of Directive 2001/83/EC and Art. 123(7) of Regulation 2019/6.

*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.*

**Brief report of the inspection activities undertaken:**

Scope of Inspection:	<i>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)</i>
Inspected area(s) and main steps/history of the inspection	<i>Each inspected area should be specified.</i>

**Activities not inspected:**

*Where necessary attention should be drawn to areas or activities not subject to inspection on this occasion.*

**Personnel met during the inspection:**

*The names and titles of key personnel met should be specified (listed in annex).*

**Inspectors findings and observations relevant to the inspection and deficiencies:**

*Relevant headings from The Rules Governing Medicinal Products in the European Union, 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.*

Headings to be used	<i>Overview of inspection findings from last inspection and the corrective action taken.</i>
New headings may be introduced when relevant	<ul style="list-style-type: none"> <li><i>Quality Management</i></li> <li><i>Personnel</i></li> <li><i>Premises and Equipment</i></li> <li><i>Documentation</i></li> <li><i>Production</i></li> <li><i>Quality Control</i></li> <li><i>Contract Manufacture and Analysis</i></li> <li><i>Complaints and Product Recall</i></li> </ul>

	<i>Self-Inspection</i>
Distribution and shipment:	<i>e.g. Compliance with Good Distribution Practice</i>
Questions raised relating to the assessment of a marketing application:	<i>e.g. Pre-authorisation inspections</i>
Other specific issues identified:	<i>e.g. Relevant future changes announced by company</i>
Site Master File:	<i>Assessment of SMF if any; date of SMF</i>

<b>Miscellaneous:</b>
Samples taken
<b>Annexes attached:</b>
<i>List of any annexes attached</i>
<b>List of deficiencies classified into critical, major and others:</b>
<i>All deficiencies should be listed and the relevant reference to the EU GMP Guide and other relevant EU Guidelines should be mentioned.</i>
<i>All deficiencies found should be listed even if corrective action has taken place straight away.</i>
<i>If the deficiencies are related to the assessment of the marketing application it should be clearly stated.</i>
<i>The company should be asked to inform the Inspectorate about the proposed time schedule for corrections and on progress.</i>
<b>Inspectors' comments on the manufacturer's response to the inspection findings:</b>
<i>i.e. are the responses acceptable?</i>
<b>Inspectors' comments on the questions/issues raised in the assessment report</b>
<b>Recommendations for further actions (if any):</b>
<i>To the Committee requesting the inspection or to the Competent / Enforcement Authority for the site inspected.</i>
<b>Summary and conclusions:</b>
<i>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 (EU) 2017/1572, Delegated Regulation (EU) 2017/1569 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).</i>

<b>Name(s):</b>	<i>The inspection report should be <b>signed and dated</b> by all inspector(s)/assessors having participated in the inspection.</i>
<b>Signatures(s):</b>	
<b>Organisation(s):</b>	
<b>Date:</b>	
Distribution of Report:	<i>For inspections requested by the European Medicines Agency the inspection report should be forwarded to the Agency.</i>

## 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;

or

which indicates a major deviation from EU Good Manufacturing Practice;

or

(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

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;

or

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).

## Union format for manufacturer's authorisation

### Table of contents:

1. Union format for manufacturer's authorisation
2. ANNEXES 1 and/or 2 - scope of authorisation
3. ANNEX 3 (Optional) - address(es) of contract manufacturing sites
4. ANNEX 4 (Optional) - address(es) of contract laboratories
5. ANNEX 5 (Optional) - name of qualified person
6. ANNEX 6 (Optional) - name of person responsible for quality control / production
7. ANNEX 7 (Optional) - date of inspection on which authorisation granted
8. ANNEX 8 (Optional) - products authorised for manufacture/import

<b>Title</b>	<b>Union format for manufacturers authorisation</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Union format for Manufacturer/Importer Authorisation<sup>1,2</sup>

1. Authorisation number
2. Name of authorisation holder
  - 2.a Alternative name of authorisation holder (optional)
3. Address(es) of manufacturing site(s)  
(All authorised sites should be listed if not covered by separate licences)
  - 3.a Additional details on units inspected of manufacturing site(s) address(es) (optional)
4. Legally registered address of authorisation holder
  - 4.a Additional details on units inspected of legally registered address (optional)
5. Scope of authorisation and dosage forms<sup>2</sup>                      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)<sup>3</sup>

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<sup>1</sup> The authorisation referred to in paragraph 40(1) of Directive 2001/83/EC as amended and Article 88(1) of Regulation (EU) 2019/6, shall also be required for imports coming from third countries into a Member State.

<sup>2</sup> Guidance on the interpretation of this template can be found in the Interpretation of the Union format for Manufacturer/Importer Authorisation

<sup>3</sup> The Competent Authority is responsible for the appropriate linking of the authorisation with the manufacturer's application (Article 42(3) of Directive 2001/83/EC as amended and Article 90(3) of Regulation (EU) 2019/6).

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**SCOPE OF AUTHORISATION** (delete the sections that do not apply)  
**ANNEX 1**

Name and address of the site:

<input type="checkbox"/> Human Medicinal Products
<input type="checkbox"/> Veterinary Medicinal Products

<b>AUTHORISED OPERATIONS</b>
<input type="checkbox"/> Manufacturing Operations (according to part 1)
<input type="checkbox"/> Importation of Medicinal Products (according to part 2)

<b>Part 1 - MANUFACTURING OPERATIONS</b>	
<b>1.1</b>	<b>Sterile products</b>
	<i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"> <li>1.1.1.1 Large volume liquids</li> <li>1.1.1.2 Lyophilisates</li> <li>1.1.1.3 Semi-solids</li> <li>1.1.1.4 Small volume liquids</li> <li>1.1.1.5 Solids and implants</li> <li>1.1.1.6 Other &lt;free text&gt;</li> </ul>
	<i>1.1.2 Terminally sterilised (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"> <li>1.1.2.1 Large volume liquids</li> <li>1.1.2.2 Semi-solids</li> <li>1.1.2.3 Small volume liquids</li> <li>1.1.2.4 Solids and implants</li> <li>1.1.2.5 Other &lt;free text&gt;</li> </ul>
	<i>1.1.3 Batch certification</i>

<b>1.2</b>	<b>Non-sterile products</b>
	<i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"> <li>1.2.1.1 Capsules, hard shell</li> <li>1.2.1.2 Capsules, soft shell</li> <li>1.2.1.3 Chewing gums</li> <li>1.2.1.4 Impregnated matrices</li> <li>1.2.1.5 Liquids for external use</li> <li>1.2.1.6 Liquids for internal use</li> <li>1.2.1.7 Medicinal gases</li> <li>1.2.1.8 Other solid dosage forms</li> <li>1.2.1.9 Pressurised preparations</li> <li>1.2.1.10 Radionuclide generators</li> </ul>

	<ul style="list-style-type: none"> <li>1.2.1.11 Semi-solids</li> <li>1.2.1.12 Suppositories</li> <li>1.2.1.13 Tablets</li> <li>1.2.1.14 Transdermal patches</li> <li>1.2.1.15 Intraruminal devices</li> <li>1.2.1.16 Veterinary premixes</li> <li>1.2.1.17 Other &lt;free text&gt;</li> </ul>
	<i>1.2.2 Batch Certification</i>
<b>1.3</b>	<b>Biological medicinal products</b>
	<p><i>1.3.1 Biological medicinal products (list of product types)</i></p> <ul style="list-style-type: none"> <li>1.3.1.1 Blood products</li> <li>1.3.1.2 Immunological products</li> <li>1.3.1.3 Cell therapy products</li> <li>1.3.1.4 Gene therapy products</li> <li>1.3.1.5 Biotechnology products</li> <li>1.3.1.6 Human or animal extracted products</li> <li>1.3.1.7 Tissue engineered products</li> <li>1.3.1.8 Other &lt;free text&gt;</li> </ul>
	<p><i>1.3.2 Batch certification (list of product types)</i></p> <ul style="list-style-type: none"> <li>1.3.2.1 Blood products</li> <li>1.3.2.2 Immunological products</li> <li>1.3.2.3 Cell therapy products</li> <li>1.3.2.4 Gene therapy products</li> <li>1.3.2.5 Biotechnology products</li> <li>1.3.2.6 Human or animal extracted products</li> <li>1.3.2.7 Tissue engineered products</li> <li>1.3.2.8 Other &lt;free text&gt;</li> </ul>
<b>1.4</b>	<b>Other products or manufacturing activity</b>
	<p><i>1.4.1 Manufacture of:</i></p> <ul style="list-style-type: none"> <li>1.4.1.1 Herbal products</li> <li>1.4.1.2 Homoeopathic products</li> <li>1.4.1.3 Other &lt;free text&gt;</li> </ul>
	<p><i>1.4.2 Sterilisation of active substances/excipients/finished product:</i></p> <ul style="list-style-type: none"> <li>1.4.2.1 Filtration</li> <li>1.4.2.2 Dry heat</li> <li>1.4.2.3 Moist heat</li> <li>1.4.2.4 Chemical</li> <li>1.4.2.5 Gamma irradiation</li> <li>1.4.2.6 Electron beam</li> </ul>
	<i>1.4.3 Other &lt;free text&gt;</i>
<b>1.5</b>	<b>Packaging</b>
	<p><i>1.5.1 Primary packaging</i></p> <ul style="list-style-type: none"> <li>1.5.1.1 Capsules, hard shell</li> <li>1.5.1.2 Capsules, soft shell</li> <li>1.5.1.3 Chewing gums</li> <li>1.5.1.4 Impregnated matrices</li> <li>1.5.1.5 Liquids for external use</li> </ul>

	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 <free text>
	<i>1.5.2 Secondary packaging</i>
<b>1.6</b>	<b>Quality control testing</b>
	<i>1.6.1 Microbiological: sterility</i>
	<i>1.6.2 Microbiological: non-sterility</i>
	<i>1.6.3 Chemical/Physical</i>
	<i>1.6.4 Biological</i>

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

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<b>Part 2 - IMPORTATION OF MEDICINAL PRODUCTS</b>	
<b>2.1</b>	<b>Quality control testing of imported medicinal products</b>
	2.1.1 <i>Microbiological: sterility</i>
	2.1.2 <i>Microbiological: non-sterility</i>
	2.1.3 <i>Chemical/Physical</i>
	2.1.4 <i>Biological</i>
<b>2.2</b>	<b>Batch certification of imported medicinal products</b>
	2.2.1 <i>Sterile Products</i> 2.2.1.1 Aseptically prepared 2.2.1.2 Terminally sterilised
	2.2.2 <i>Non-sterile products</i>
	2.2.3 <i>Biological medicinal products</i> 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 <free text >
<b>2.3</b>	<b>Other importation activities</b> (any other importation activity that is not covered above)
	2.3.1 <i>Site of physical importation</i>
	2.3.2 <i>Importation of intermediate which undergoes further processing</i>
	2.3.3 <i>Biological active substance</i>
	2.3.4 <i>Other &lt;free text&gt;</i>

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

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

**ANNEX 2**

Name and address of the site:

<input type="checkbox"/> Human Investigational Medicinal Products (optional)
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AUTHORISED OPERATIONS
<input type="checkbox"/> Manufacturing Operations of Investigational Medicinal Products (according to part 1)
<input type="checkbox"/> Importation of Investigational Medicinal Products (according to part 2)

<b>Part 1 - MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS</b>	
<b>1.1</b>	<b>Sterile investigational medicinal products</b>
	<p><i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.1.1.1 Large volume liquids</li> <li>1.1.1.2 Lyophilisates</li> <li>1.1.1.3 Semi-solids</li> <li>1.1.1.4 Small volume liquids</li> <li>1.1.1.5 Solids and implants</li> <li>1.1.1.6 Other &lt;free text&gt;</li> </ul>
	<p><i>1.1.2 Terminally sterilised (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.1.2.1 Large volume liquids</li> <li>1.1.2.2 Semi-solids</li> <li>1.1.2.3 Small volume liquids</li> <li>1.1.2.4 Solids and implants</li> <li>1.1.2.5 Other &lt;free text&gt;</li> </ul>
	<p><i>1.1.3 Batch certification</i></p>

<b>1.2</b>	<b>Non-sterile investigational medicinal products</b>
	<p><i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.2.1.1 Capsules, hard shell</li> <li>1.2.1.2 Capsules, soft shell</li> <li>1.2.1.3 Chewing gums</li> <li>1.2.1.4 Impregnated matrices</li> <li>1.2.1.5 Liquids for external use</li> <li>1.2.1.6 Liquids for internal use</li> <li>1.2.1.7 Medicinal gases</li> <li>1.2.1.8 Other solid dosage forms</li> <li>1.2.1.9 Pressurised preparations</li> <li>1.2.1.10 Radionuclide generators</li> <li>1.2.1.11 Semi-solids</li> <li>1.2.1.12 Suppositories</li> <li>1.2.1.13 Tablets</li> </ul>

	1.2.1.14 Transdermal patches 1.2.1.17 Other <free text>
	<i>1.2.2 Batch certification</i>
<b>1.3</b>	<b>Biological investigational medicinal products</b>
	<i>1.3.1 Biological medicinal products (list of product types)</i> 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 <free text>
	<i>1.3.2 Batch certification (list of product types)</i> 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 <free text>
<b>1.4</b>	<b>Other investigational medicinal products or manufacturing activity</b>
	<i>1.4.1 Manufacture of:</i> 1.4.1.1 Herbal products 1.4.1.2 Homoeopathic products 1.4.1.3 Other <free text>
	<i>1.4.2 Sterilisation of active substances/excipients/finished product:</i> 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
	<i>1.4.3 Other &lt;free text&gt;</i>
<b>1.5</b>	<b>Packaging</b>
	<i>1.5.1 Primary packaging</i> 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 <free text>
	<i>1.5.2 Secondary packaging</i>
<b>1.6</b>	<b>Quality control testing</b>
	<i>1.6.1 Microbiological: sterility</i>
	<i>1.6.2 Microbiological: non-sterility</i>
	<i>1.6.3 Chemical/Physical</i>
	<i>1.6.4 Biological</i>

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

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<b>Part 2 - IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS</b>	
<b>2.1</b>	<b>Quality control testing of imported investigational medicinal products</b>
	2.1.1 <i>Microbiological: sterility</i>
	2.1.2 <i>Microbiological: non-sterility</i>
	2.1.3 <i>Chemical/Physical</i>
	2.1.4 <i>Biological</i>
<b>2.2</b>	<b>Batch certification of imported investigational medicinal products</b>
	2.2.1 <i>Sterile Products</i>
	2.2.1.1 Aseptically prepared
	2.2.1.2 Terminally sterilised
	2.2.2 <i>Non-sterile products</i>
	2.2.3 <i>Biological products</i>
	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 <free text>
<b>2.3</b>	<b>Other importation activities</b>
	2.3.1 <i>Site of physical importation</i>
	2.3.2 <i>Importation of intermediate which undergoes further processing</i>
	2.3.3 <i>Biological active substance</i>
	2.3.4 <i>Other &lt;free text&gt;</i>

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)**

Date of Inspection on which authorisation was granted      dd / mm / yyyy \_\_\_\_\_

Scope of last Inspection

.....  
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.....

**ANNEX 8 (Optional)**

Products authorised to be manufactured/imported (in accordance with Articles 41 and 42 of Directive 2001/83/EC, as amended or Articles 89 and 90 of Regulation (EU) 2019/6).

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## Union format for a GMP certificate

<b>Title</b>	<b>Union format for a GMP certificate</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# Union format for a GMP certificate

(LETTERHEAD OF COMPETENT AUTHORITY)

Certificate No: \_\_\_/\_\_\_/\_\_\_

## CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER<sup>1,2</sup>

### Part 1

**Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC or Art. 94(1) of Regulation (EU) 2019/6 or Article 63(4) of Regulation (EU) No 536/2014\***

*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 .....

Manufacturer's alternative name .....

Site address.....

Additional details on units inspected.....

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. .... in accordance with Art. 40 of Directive 2001/83/EC transposed in the following national legislation:

....., or Art. 88 of Regulation (EU) 2019/6 or Art. 61(1) of Regulation (EU) No 536/2014\*

*or*

Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 8(2)/19(3) of Regulation (EC) 726/2004\*, or Art. 94(4)/123 of Regulation (EU) 2019/6 or Art. 111(4) of Directive 2001/83/EC transposed in the following national legislation:

..... \*

*and/or\**

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation:

.....\* and/or

Art. 123 (1) to (6) of Regulation (EU) 2019/6\*

*and/or\**

Is an excipient manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC\* transposed in the following national legislation:

..... \*

*and/or\**

Is an investigational medicinal product manufacturer that has been inspected in accordance with Art. 63 of Regulation (EU) No 536/2014 and/or GMP for investigational medicinal products for veterinary use in accordance with the following national legislation:

..... \*

*or*

<sup>1</sup> The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 94(1) of Regulation (EU) 2019/6 is also applicable to importers.

<sup>2</sup> Guidance on the interpretation of this template can be found in the Interpretation of the Union format for GMP certificate.

Other (please specify): .....\*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ...../...../..... [date], it is considered that it complies with the Good Manufacturing Practice requirements<sup>1</sup> referred to in the Agreement of Mutual Recognition between the European Union and [MRA partner]/ The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569, as appropriate / The principles and guidelines of Good Manufacturing Practice laid down in Directive 91/412/EEC<sup>3</sup>/ The principles of GMP for active substances<sup>3</sup> referred to in Article 47 of Directive 2001/83/EC / Article 93(2) of Regulation 2019/6.\* an appropriate level of GMP as referred to in Article 46(f) of Directive 2001/83/EC and Art. 93(1)(j) of Regulation (EU) 2019/6.

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. Updates to restrictions or clarifying remarks can be identified through the EudraGMDP website (<http://eudragmdp.ema.europa.eu/>).

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 EudraGMDP. 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\*

<b>1.1</b>	<b>Sterile products</b>
	<i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"><li>1.1.1.1 Large volume liquids</li><li>1.1.1.2 Lyophilisates</li><li>1.1.1.3 Semi-solids</li><li>1.1.1.4 Small volume liquids</li><li>1.1.1.5 Solids and implants</li><li>1.1.1.6 Other &lt;free text&gt;</li></ul>
	<i>1.1.2 Terminally sterilised (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"><li>1.1.2.1 Large volume liquids</li><li>1.1.2.2 Semi-solids</li><li>1.1.2.3 Small volume liquids</li><li>1.1.2.4 Solids and implants</li><li>1.1.2.5 Other &lt;free text&gt;</li></ul>
	<i>1.1.3 Batch certification</i>
<b>1.2</b>	<b>Non-sterile products</b>
	<i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i> <ul style="list-style-type: none"><li>1.2.1.1 Capsules, hard shell</li><li>1.2.1.2 Capsules, soft shell</li><li>1.2.1.3 Chewing gums</li><li>1.2.1.4 Impregnated matrices</li><li>1.2.1.5 Liquids for external use</li><li>1.2.1.6 Liquids for internal use</li><li>1.2.1.7 Medicinal gases</li><li>1.2.1.8 Other solid dosage forms</li><li>1.2.1.9 Pressurised preparations</li><li>1.2.1.10 Radionuclide generators</li><li>1.2.1.11 Semi-solids</li><li>1.2.1.12 Suppositories</li><li>1.2.1.13 Tablets</li><li>1.2.1.14 Transdermal patches</li><li>1.2.1.15 Intraruminal devices</li><li>1.2.1.16 Veterinary premixes</li><li>1.2.1.17 Other &lt;free text&gt;</li></ul>
	<i>1.2.2 Batch certification</i>

<b>1.3</b>	<b>Biological medicinal products</b>
	<p><i>1.3.1 Biological medicinal products</i></p> <ul style="list-style-type: none"> <li>1.3.1.1 Blood products</li> <li>1.3.1.2 Immunological products</li> <li>1.3.1.3 Cell therapy products</li> <li>1.3.1.4 Gene therapy products</li> <li>1.3.1.5 Biotechnology products</li> <li>1.3.1.6 Human or animal extracted products</li> <li>1.3.1.7 Tissue engineered products</li> <li>1.3.1.8 Other &lt;free text&gt;</li> </ul>
	<p><i>1.3.2 Batch certification (list of product types)</i></p> <ul style="list-style-type: none"> <li>1.3.2.1 Blood products</li> <li>1.3.2.2 Immunological products</li> <li>1.3.2.3 Cell therapy products</li> <li>1.3.2.4 Gene therapy products</li> <li>1.3.2.5 Biotechnology products</li> <li>1.3.2.6 Human or animal extracted products</li> <li>1.3.2.7 Tissue engineered products</li> <li>1.3.2.8 Other &lt;free text&gt;</li> </ul>
<b>1.4</b>	<b>Other products or processing activity</b>
	<p><i>1.4.1 Manufacture of:</i></p> <ul style="list-style-type: none"> <li>1.4.1.1 Herbal products</li> <li>1.4.1.2 Homoeopathic products</li> <li>1.4.1.3 Other &lt;free text &gt;</li> </ul>
	<p><i>1.4.2 Sterilisation of active substances/excipients/finished product:</i></p> <ul style="list-style-type: none"> <li>1.4.2.1 Filtration</li> <li>1.4.2.2 Dry heat</li> <li>1.4.2.3 Moist heat</li> <li>1.4.2.4 Chemical</li> <li>1.4.2.5 Gamma irradiation</li> <li>1.4.2.6 Electron beam</li> </ul>
	<p><i>1.4.3 Others &lt;free text&gt;</i></p>
<b>1.5</b>	<b>Packaging</b>
	<p><i>1.5.1 Primary packing</i></p> <ul style="list-style-type: none"> <li>1.5.1.1 Capsules, hard shell</li> <li>1.5.1.2 Capsules, soft shell</li> <li>1.5.1.3 Chewing gums</li> <li>1.5.1.4 Impregnated matrices</li> <li>1.5.1.5 Liquids for external use</li> <li>1.5.1.6 Liquids for internal use</li> <li>1.5.1.7 Medicinal gases</li> <li>1.5.1.8 Other solid dosage forms</li> <li>1.5.1.9 Pressurised preparations</li> <li>1.5.1.10 Radionuclide generators</li> <li>1.5.1.11 Semi-solids</li> <li>1.5.1.12 Suppositories</li> <li>1.5.1.13 Tablets</li> <li>1.5.1.14 Transdermal patches</li> <li>1.5.1.15 Intraruminal devices</li> <li>1.5.1.16 Veterinary premixes</li> <li>1.5.1.17 Other &lt;free text&gt;</li> </ul>
	<p><i>1.5.2 Secondary packing</i></p>

<b>1.6</b>	<b>Quality control testing</b>
	<i>1.6.1 Microbiological: sterility</i>
	<i>1.6.2 Microbiological: non-sterility</i>
	<i>1.6.3 Chemical/Physical</i>
	<i>1.6.4 Biological</i>

**2 IMPORTATION OF MEDICINAL PRODUCTS\***

**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 <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 this certificate\*:

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 .....



<b>3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES</b>	
Active Substance(s):	
<b>3.1</b>	<b>Manufacture of Active Substance by Chemical Synthesis</b>
	3.1.1 <i>Manufacture of active substance intermediates</i> 3.1.2 <i>Manufacture of crude active substance</i> 3.1.3 <i>Salt formation / Purification steps: &lt;free text&gt; (e.g. crystallisation)</i> 3.1.4 <i>Other &lt;free text&gt;</i>
<b>3.2</b>	<b>Extraction of Active Substance from Natural Sources</b>
	3.2.1 <i>Extraction of substance from plant source</i> 3.2.2 <i>Extraction of substance from animal source</i> 3.2.3 <i>Extraction of substance from human source</i> 3.2.4 <i>Extraction of substance from mineral source</i> 3.2.5 <i>Modification of extracted substance &lt;specify source 1,2,3,4&gt;</i> 3.2.6 <i>Purification of extracted substance &lt;specify source 1,2,3,4 &gt;</i> 3.2.7 <i>Other &lt;free text&gt;</i>
<b>3.3</b>	<b>Manufacture of Active Substance using Biological Processes</b>
	3.3.1 <i>Fermentation</i> 3.3.2 <i>Cell Culture &lt;specify cell type&gt; (e.g. mammalian / bacterial)</i> 3.3.3 <i>Isolation / Purification</i> 3.3.4 <i>Modification</i> 3.3.5 <i>Other &lt;free text&gt;</i>
<b>3.4</b>	<b>Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)</b>
	3.4.1 <i>Aseptically prepared</i> 3.4.2 <i>Terminally sterilised</i>
<b>3.5</b>	<b>General Finishing Steps</b>
	3.5.1 <i>Physical processing steps &lt;specify &gt; (e.g. drying, milling / micronisation, sieving)</i> 3.5.2 <i>Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</i> 3.5.3 <i>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)</i> 3.5.4 <i>Other &lt;free text&gt; (for operations not described above)</i>
<b>3.6</b>	<b>Quality Control Testing</b>
	3.6.1 <i>Physical / Chemical testing</i> 3.6.2 <i>Microbiological testing (excluding sterility testing)</i> 3.6.3 <i>Microbiological testing (including sterility testing)</i> 3.6.4 <i>Biological Testing</i>

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**4. OTHER ACTIVITIES - ACTIVE SUBSTANCES**  
<free text>

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]<sup>1</sup>  
.....  
.....  
[name, title, national authority, phone number and e-mail]

(\*): delete that which does not apply

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

# Statement of non-compliance with GMP

## Table of contents:

1. Union format for a statement of non-compliance with GMP

<b>Title</b>	<b>Statement of non-compliance with GMP</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	The version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

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(LETTERHEAD OF COMPETENT AUTHORITY)

Report No: \_\_ \_ / \_\_ \_ / \_\_ \_ / \_\_ \_

## 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<sup>1</sup>**

### Part 1

Issued following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC (*Human Medicines*), Art. 94(2) of Regulation (EU) 2019/6 (*Veterinary Medicines*) or Article 63(4) of Regulation (EU) No 536/2014 (*Investigational Medicinal Products*).\*

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

The manufacturer: .....

Manufacturer's alternative name: .....

Site address .....

Additional details on units inspected:

.....

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on .... / ..... / ..... [date], 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 Directive (EU) 2017/1572 (*GMP for Human Medicines*)/ Commission Delegated Regulation (EU) 2017/1569 (*GMP for Investigational Human Medicines*)/ Directive 91/412/EEC (*GMP for Veterinary Medicines*)/ the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC (*GMP for Active Substances in Human Medicines*) / Article 93(2) of Regulation (EU) 2019/6 (*GMP for Active Substances in Veterinary Medicines*) / an appropriate level of GMP as referred to in Article 46(f) of Directive 2001/83/EC (*GMP for Active Substances in Human Medicines*)\* and Article 93(1) (j) to (l) of Regulation (EU) 2019/6 (*GMP for Active Substances in Veterinary Medicines*)

Note to receiving authorities: Please contact the issuing authority within 20 working days in case there are critical<sup>2</sup> medicinal products potentially affected by this statement.

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<sup>1</sup> The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and Art. 94(2) of Regulation (EU) 2019/6, as amended, is also applicable to importers.

<sup>2</sup> See Appendix 3 of the relevant procedure in the Compilation of Union Procedures

Manufacturing Authorisation Holders directly affected by this statement have failed to comply with their obligations under Art. 46 of Directive 2001/83/EC or Art. 93(1)(j) to (l) of Regulation (EU) 2019/6 and as a consequence the Qualified Person referred to in Art. 48 of Directive 2001/83/EC and Art. 97(1) of Regulation (EU) 2019/6 is unable to perform the batch certification referred to in Art. 51 of Directive 2001/83/EC and Art. 97 (6) and (7) of Regulation (EU) 2019/6.

In exceptional circumstances there may be no objection to the Qualified Person certifying affected batches thereby allowing their release provided all of the following conditions are fulfilled:

1. Batch certification is performed in order to maintain supply of critical medicinal products only.
2. A documented risk assessment has been performed by, or on behalf of, the Qualified Person and additional actions have been implemented by the manufacturing and/or batch release site to mitigate the risks posed by the non-compliance. Note: Repeated testing alone is not normally sufficient risk mitigation but, together with other actions, can form part of a strategy commensurate with the nature and the level of risk.
3. A thorough risk-benefit evaluation has been performed for the acceptance of risk and a report prepared that takes full account of the nature of the non-compliance with the involvement of:

Figure: 1. The Manufacturing Authorisation Holder and the Qualified Person of the site responsible for batch certification

Figure: 2. The manufacturing site subject to this Statement of Non-Compliance, if different from the above

Figure: 3. The relevant Marketing Authorisation Holder(s)

The report has been shared with the National Competent Authorities of the countries in which distribution of the affected batches is anticipated and that any comments from those authorities have been taken into account.

4. Written confirmation has been obtained from the National Competent Authorities in whose territories the affected batches are intended to be distributed that the product is considered critical on its territory, and that there is no objection to distribution. **Note: Responsibility for batch certification remains with the Qualified Person.**
5. The Supervisory Authority has been informed, if different from the above, and it has not suspended or revoked the relevant Manufacturing Authorisation
6. The affected Marketing Authorisations have not been revoked or suspended.
7. Any further conditions imposed by the Supervisory Authority and other involved National Competent Authorities are met

## Part 2

*In the sections below, highlight the manufacturer's activities that the NCS is relevant to.*

<input type="checkbox"/> Human Medicinal Products*
<input type="checkbox"/> Veterinary Medicinal Products*
<input type="checkbox"/> Human Investigational Medicinal Products*

<b>1 NON-COMPLIANT MANUFACTURING OPERATIONS- MEDICINAL PRODUCTS*</b>	
<b>1.1</b>	<b>Sterile Products</b>
	<p><i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.1.1.1 Large volume liquids</li> <li>1.1.1.2 Lyophilisates</li> <li>1.1.1.3 Semi-solids</li> <li>1.1.1.4 Small volume liquids</li> <li>1.1.1.5 Solids and implants</li> <li>1.1.1.6 Other &lt;free text&gt;</li> </ul>
	<p><i>1.1.2 Terminally sterilised (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.1.2.1 Large volume liquids</li> <li>1.1.2.2 Semi-solids</li> <li>1.1.2.3 Small volume liquids</li> <li>1.1.2.4 Solids and implants</li> <li>1.1.2.5 Other &lt;free text&gt;</li> </ul>
	<i>1.1.3 Batch certification</i>
<b>1.2</b>	<b>Non-sterile products</b>
	<p><i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i></p> <ul style="list-style-type: none"> <li>1.2.1.1 Capsules, hard shell</li> <li>1.2.1.2 Capsules, soft shell</li> <li>1.2.1.3 Chewing gums</li> <li>1.2.1.4 Impregnated matrices</li> <li>1.2.1.5 Liquids for external use</li> <li>1.2.1.6 Liquids for internal use</li> <li>1.2.1.7 Medicinal gases</li> <li>1.2.1.8 Other solid dosage forms</li> <li>1.2.1.9 Pressurised preparations</li> <li>1.2.1.10 Radionuclide generators</li> <li>1.2.1.11 Semi-solids</li> <li>1.2.1.12 Suppositories</li> <li>1.2.1.13 Tablets</li> <li>1.2.1.14 Transdermal patches</li> <li>1.2.1.15 Intraruminal devices</li> <li>1.2.1.16 Veterinary premixes</li> <li>1.2.1.17 Other &lt;free text&gt;</li> </ul>
	<i>1.2.2 Batch certification</i>
<b>1.3</b>	<b>Biological medicinal products</b>

	<p><b>1.3.1 Biological medicinal products</b></p> <ul style="list-style-type: none"> <li>1.3.1.1 Blood products</li> <li>1.3.1.2 Immunological products</li> <li>1.3.1.3 Cell therapy products</li> <li>1.3.1.4 Gene therapy products</li> <li>1.3.1.5 Biotechnology products</li> <li>1.3.1.6 Human or animal extracted products</li> <li>1.3.1.7 Tissue engineered products</li> <li>1.3.1.8 Other &lt;free text&gt;</li> </ul>
	<p><b>1.3.2 Batch certification (list of product types)</b></p> <ul style="list-style-type: none"> <li>1.3.2.1 Blood products</li> <li>1.3.2.2 Immunological products</li> <li>1.3.2.3 Cell therapy products</li> <li>1.3.2.4 Gene therapy products</li> <li>1.3.2.5 Biotechnology products</li> <li>1.3.2.6 Human or animal extracted products</li> <li>1.3.2.7 Tissue engineered products</li> <li>1.3.2.8 Other &lt;free text&gt;</li> </ul>
<b>1.4</b>	<b>Other products or manufacturing activity</b>
	<p><b>1.4.1 Manufacture of:</b></p> <ul style="list-style-type: none"> <li>1.4.1.1 Herbal products</li> <li>1.4.1.2 Homoeopathic products</li> <li>1.4.1.3 Other &lt;free text&gt;</li> </ul>
	<p><b>1.4.2 Sterilisation of active substances/excipients/finished product:</b></p> <ul style="list-style-type: none"> <li>1.4.2.1 Filtration</li> <li>1.4.2.2 Dry heat</li> <li>1.4.2.3 Moist heat</li> <li>1.4.2.4 Chemical</li> <li>1.4.2.5 Gamma irradiation</li> <li>1.4.2.6 Electron beam</li> </ul>
	<p><b>1.4.3 Others &lt;free text&gt;</b></p>
<b>1.5</b>	<b>Packaging</b>
	<p><b>1.5.1 Primary packing</b></p> <ul style="list-style-type: none"> <li>1.5.1.1 Capsules, hard shell</li> <li>1.5.1.2 Capsules, soft shell</li> <li>1.5.1.3 Chewing gums</li> <li>1.5.1.4 Impregnated matrices</li> <li>1.5.1.5 Liquids for external use</li> <li>1.5.1.6 Liquids for internal use</li> <li>1.5.1.7 Medicinal gases</li> <li>1.5.1.8 Other solid dosage forms</li> <li>1.5.1.9 Pressurised preparations</li> <li>1.5.1.10 Radionuclide generators</li> <li>1.5.1.11 Semi-solids</li> <li>1.5.1.12 Suppositories</li> <li>1.5.1.13 Tablets</li> <li>1.5.1.14 Transdermal patches</li> <li>1.5.1.15 Intraruminal devices</li> <li>1.5.1.16 Veterinary premixes</li> <li>1.5.1.17 Other &lt;free text&gt;</li> </ul>
	<p><b>1.5.2 Secondary packing</b></p>
<b>1.6</b>	<b>Quality control testing</b>
	<p><b>1.6.1 Microbiological: sterility</b></p>

	1.6.2 <i>Microbiological: non-sterility</i>
	1.6.3 <i>Chemical/Physical</i>
	1.6.4 <i>Biological</i>

<b>2 NON-COMPLIANT IMPORTATION OPERATIONS*</b>	
<b>2.1</b>	<b>Quality control testing of imported medicinal products</b>
	2.1.1 <i>Microbiological: sterility</i>
	2.1.2 <i>Microbiological: non-sterility</i>
	2.1.3 <i>Chemical/Physical</i>
	2.1.4 <i>Biological</i>
<b>2.2</b>	<b>Batch certification of imported medicinal products</b>
	2.2.1 <i>Sterile Products</i> 2.2.1.1 Aseptically prepared 2.2.1.2 Terminally sterilised
	2.2.2 <i>Non-sterile products</i>
	2.2.3 <i>Biological medicinal products</i> 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 <free text>
<b>2.3</b>	<b>Other importation activities</b>
	2.3.1 <i>Site of physical importation</i>
	2.3.2 <i>Importation of intermediate which undergoes further processing</i>
	2.3.3 <i>Biological active substance</i>
	2.3.4 <i>Other &lt;free text&gt;</i>

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

*Clarification should be provided as to why the scope of NCS is limited, such as non-compliance of partial site activities (e.g. activities regarding sterility assurance are non-compliant but non sterile manufacturing activities are deemed compliant); or targeted inspection (e.g. sterile products inspection at a site manufacturing both sterile and non-sterile dosage forms),*

.....  
 .....



<b>3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES</b>	
Active Substance(s):	
<b>3.1</b>	<b>Manufacture of Active Substance by Chemical Synthesis</b>
	3.1.1 <i>Manufacture of active substance intermediates</i> 3.1.2 <i>Manufacture of crude active substance</i> 3.1.3 <i>Salt formation / Purification steps: &lt;free text&gt; (e.g. crystallisation)</i> 3.1.4 <i>Other &lt;free text&gt;</i>
<b>3.2</b>	<b>Extraction of Active Substance from Natural Sources</b>
	3.2.1 <i>Extraction of substance from plant source</i> 3.2.2 <i>Extraction of substance from animal source</i> 3.2.3 <i>Extraction of substance from human source</i> 3.2.4 <i>Extraction of substance from mineral source</i> 3.2.5 <i>Modification of extracted substance &lt;specify source 1,2,3,4&gt;</i> 3.2.6 <i>Purification of extracted substance &lt;specify source 1,2,3,4 &gt;</i> 3.2.7 <i>Other &lt;free text&gt;</i>
<b>3.3</b>	<b>Manufacture of Active Substance using Biological Processes</b>
	3.3.1 <i>Fermentation</i> 3.3.2 <i>Cell Culture &lt;specify cell type&gt; (e.g. mammalian / bacterial )</i> 3.3.3 <i>Isolation / Purification</i> 3.3.4 <i>Modification</i> 3.3.5 <i>Other &lt;free text&gt;</i>
<b>3.4</b>	<b>Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)</b>
	3.4.1 <i>Aseptically prepared</i> 3.4.2 <i>Terminally sterilised</i>
<b>3.5</b>	<b>General Finishing Steps</b>
	3.5.1 <i>Physical processing steps &lt; specify &gt; (e.g. drying, milling / micronisation, sieving)</i> 3.5.2 <i>Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</i> 3.5.3 <i>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)</i> 3.5.4 <i>Other &lt;free text&gt; (for operations not described above)</i>
<b>3.6</b>	<b>Quality Control Testing</b>
	3.6.1 <i>Physical / Chemical testing</i> 3.6.2 <i>Microbiological testing (excluding sterility testing)</i> 3.6.3 <i>Microbiological testing (including sterility testing)</i> 3.6.4 <i>Biological Testing</i>

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<b>4. OTHER ACTIVITIES- ACTIVE SUBSTANCES</b>  <free text>
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Any restrictions or clarifying remarks related to the scope of this statement\*:  
*Clarification should be provided as to why the scope of NCS is limited, e.g. non-compliance of partial site activities; targeted inspection*

.....

.....

## Part 3

### 1. Nature of non-compliance

<free text>

*EudraGMDP allows only 999 characters*

*State a brief summary of the critical and major deficiency / deficiencies that have led to the NCS being issued, e.g:*

*"Failure to manage GMP changes, risks of cross contamination between hazardous products, failure to control sterilisation processes"*

*GMP deficiencies which did not influence the decision to issue the NCS should not be described.*

*Keep the description factual, concise and based on the non-conformance(s) reported to the manufacturer.*

*Consider possible interpretation issues when describing deficiencies and making recommendations.*

.....  
.....

### 2. Action taken/proposed by the NCA

*EudraGMDP requires a text entry for any 'checked boxes'. Any text entry requires the relevant box to be checked.*

Suspension/variation/revocation\* of the manufacturing authorisation No. .... in full/in part\*

<free text> *State any proposed (or taken) action on the manufacturing authorisation. If so, state the action and timescale involved.* .....

.....

Restriction of current valid GMP certificate No. ....

<free text> *State the current GMP certificate reference and if any restriction / withdrawal is proposed or already actioned, with explanation (e.g. issued for other compliant activities).* .....

*In most cases, NCS becomes effective from the date of publication on EudraGMDP. If the NCA recommends that the NCS be applied retrospectively to batches previously manufactured (but not yet QP certified or released to the market), this should be clearly stated, with rationale.*

.....

Suspension/revocation/requested variation/ refusal to grant \* of Marketing Authorisation(s)

<free text> *The issuing authority may make recommendations for action against affected marketing authorisations. This should be described in the context of the impact of GMP deficiency on product quality or safety. Recommendations should be stated in a manner which permits flexibility in decision-making at national and Union level, taking into account product criticality.*

*Avoid statements such as "recommendation that MA should be suspended". Instead consider "action against affected MAs should be considered where potential quality defect has greater impact to public health than supply restriction in affected Member State(s)". Refer to guidance on Regulatory Risk Assessment for advice.*

.....

.....

Recall of batches already released (separate Rapid Alert to follow)

<free text> *State if there is evidence or significant risk of defective product on the market. Is recall recommended or is it not considered necessary? Where possible, agree text with the authority leading quality defect assessments.*

*Recommendations to other Member States should usually be limited to 'consideration of recall, following NCA assessment of potential quality defect vs. supply restriction'.* .....

.....

Prohibition of supply  
 <free text> *Are any restrictions on supply recommended whilst the NCS is in force? For example, no further batches to be supplied to the market.* .....

Suspension or voiding of CEP (action to be taken by EDQM)  
 <free text> *If action against a CEP may be considered, liaise with EDQM to agree the wording for this section.* .....

Suspension of clinical trials  
 <free text> *The issuing authority may make recommendations for suspension of clinical trials. This should be described in the context of the impact of GMP deficiency on investigational product quality or safety, or trial data validity. Recommendations should be stated in a manner which permits flexibility in decision-making at national and Union level, taking into account clinical trial criticality.* .....

Others <free text>  
 <free text> *State any other relevant information that is not already covered, e.g. information on supply of unauthorised products under Art 5(1).* .....

3. Additional comments  
 <free text> *EudraGMDP allows only 999 characters. Use this field to add further explanation to support compliance or product quality risks related to the GMP deficiencies. Also use to provide rationale for any NCS scope restrictions.*  
 .....

Teleconference Date		Teleconference Time (CET)	Dial in no.
<b>Products manufactured at site, if known</b>	<b>Product</b>	<b>Dosage Form</b>	<b>Reference Member State, National or EMEA</b>
Human medicinal product(s)			
Veterinary medicinal product(s)			
Investigational medicinal product(s)	<b>EudraCT/CTIS nos.</b>		

*Guidance: where complete product lists and/or EudraCT numbers cannot be confirmed, a statement should be added to alert NCAs that the information may not be exhaustive.*

...../...../..... [date] Name and signature of the authorised person of the Competent Authority of [country]<sup>1</sup>

[Name, title, national authority, phone numbers and e-mail in case of enquiries]

<sup>1</sup> The signature, date and contact details should appear on each page of the non-compliance document.

# Notification of serious GMP non-compliance information originating from third country authorities or international organisations

## Table of contents:

1. Union format for a notification of serious GMP non-compliance information originating from third country authorities or international organisations

<b>Title</b>	<b>Notification of serious GMP non-compliance information originating from third country authorities or international organisations</b>
Date of adoption	May 2012
Date of entry into force	By end November 2012
Supersedes	Not Applicable
Reason for revision	Not Applicable, new guideline
Notes	Not applicable

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(LETTERHEAD OF COMPETENT AUTHORITY)

Report No: \_\_/\_\_/\_\_/\_

## Notification of serious GMP non-compliance information originating from third country authorities or international organisations<sup>1</sup>

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 CoUP 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\*

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<sup>1</sup> To be filled in following the 'Procedure for Dealing with Serious GMP Non-Compliance Information Originating from Third Country Authorities or International Organisations'

## Part 2

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

• <b>NON-COMPLIANT MANUFACTURING OPERATIONS – MEDICINAL PRODUCTS*</b>	
<b>1.1</b>	<b>Sterile Products</b>
	<p><i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i></p> <p>1.1.1.1 Large volume liquids</p> <p>1.1.1.2 Lyophilisates</p> <p>1.1.1.3 Semi-solids</p> <p>1.1.1.4 Small volume liquids</p> <p>1.1.1.5 Solids and implants</p> <p>1.1.1.6 Other &lt;free text&gt;</p>
	<p><i>1.1.2 Terminally sterilised (processing operations for the following dosage forms)</i></p> <p>1.1.2.1 Large volume liquids</p> <p>1.1.2.2 Semi-solids</p> <p>1.1.2.3 Small volume liquids</p> <p>1.1.2.4 Solids and implants</p> <p>1.1.2.5 Other &lt;free text&gt;</p>
	<i>1.1.3 Batch certification</i>
<b>1.2</b>	<b>Non-sterile products</b>
	<p><i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i></p> <p>1.2.1.1 Capsules, hard shell</p> <p>1.2.1.2 Capsules, soft shell</p> <p>1.2.1.3 Chewing gums</p> <p>1.2.1.4 Impregnated matrices</p> <p>1.2.1.5 Liquids for external use</p> <p>1.2.1.6 Liquids for internal use</p> <p>1.2.1.7 Medicinal gases</p> <p>1.2.1.8 Other solid dosage forms</p> <p>1.2.1.9 Pressurised preparations</p> <p>1.2.1.10 Radionuclide generators</p> <p>1.2.1.11 Semi-solids</p> <p>1.2.1.12 Suppositories</p> <p>1.2.1.13 Tablets</p> <p>1.2.1.14 Transdermal patches</p> <p>1.2.1.15 Intraruminal devices</p> <p>1.2.1.16 Veterinary premixes</p> <p>1.2.1.17 Other &lt;free text&gt;</p>
	<i>1.2.2 Batch certification</i>
<b>1.3</b>	<b>Biological medicinal products</b>

	<p><b>1.3.1 Biological medicinal products</b></p> <ul style="list-style-type: none"> <li>1.3.1.1 Blood products</li> <li>1.3.1.2 Immunological products</li> <li>1.3.1.3 Cell therapy products</li> <li>1.3.1.4 Gene therapy products</li> <li>1.3.1.5 Biotechnology products</li> <li>1.3.1.6 Human or animal extracted products</li> <li>1.3.1.7 Tissue engineered products</li> <li>1.3.1.8 Other &lt;free text &gt;</li> </ul>
	<p><b>1.3.2 Batch certification (list of product types)</b></p> <ul style="list-style-type: none"> <li>1.3.2.1 Blood products</li> <li>1.3.2.2 Immunological products</li> <li>1.3.2.3 Cell therapy products</li> <li>1.3.2.4 Gene therapy products</li> <li>1.3.2.5 Biotechnology products</li> <li>1.3.2.6 Human or animal extracted products</li> <li>1.3.2.7 Tissue engineered products</li> <li>1.3.2.8 Other &lt;free text &gt;</li> </ul>
<b>1.4</b>	<b>Other products or manufacturing activity</b>
	<p><b>1.4.1 Manufacture of:</b></p> <ul style="list-style-type: none"> <li>1.4.1.1 Herbal products</li> <li>1.4.1.2 Homoeopathic products</li> <li>1.4.1.4 Other &lt;free text &gt;</li> </ul>
	<p><b>1.4.2 Sterilisation of active substances/excipients/finished product:</b></p> <ul style="list-style-type: none"> <li>1.4.2.1 Filtration</li> <li>1.4.2.2 Dry heat</li> <li>1.4.2.3 Moist heat</li> <li>1.4.2.4 Chemical</li> <li>1.4.2.5 Gamma irradiation</li> <li>1.4.2.6 Electron beam</li> </ul>
	<p><b>1.4.3 Others &lt;free text&gt;</b></p>
<b>1.5</b>	<b>Packaging</b>



	<p><i>1.5.1 Primary packaging</i></p> <p>1.5.1.1 Capsules, hard shell</p> <p>1.5.1.2 Capsules, soft shell</p> <p>1.5.1.3 Chewing gums</p> <p>1.5.1.4 Impregnated matrices</p> <p>1.5.1.5 Liquids for external use</p> <p>1.5.1.6 Liquids for internal use</p> <p>1.5.1.7 Medicinal gases</p> <p>1.5.1.8 Other solid dosage forms</p> <p>1.5.1.9 Pressurised preparations</p> <p>1.5.1.10 Radionuclide generators</p> <p>1.5.1.11 Semi-solids</p> <p>1.5.1.12 Suppositories</p> <p>1.5.1.13 Tablets</p> <p>1.5.1.14 Transdermal patches</p> <p>1.5.1.15 Intraruminal devices</p> <p>1.5.1.16 Veterinary premixes</p> <p>1.5.1.17 Other &lt;free text &gt;</p>
	<i>1.5.2 Secondary packaging</i>
<b>1.6</b>	<b>Quality control testing</b>
	<i>1.6.1 Microbiological: sterility</i>
	<i>1.6.2 Microbiological: non-sterility</i>
	<i>1.6.3 Chemical/Physical</i>
	<i>1.6.4 Biological</i>
	<ul style="list-style-type: none"> <li>•</li> <li>• <b>NON-COMPLIANT IMPORTATION OPERATIONS*</b></li> </ul>
<b>2.1</b>	<b>Quality control testing of imported medicinal products</b>
	<i>2.1.1 Microbiological: sterility</i>
	<i>2.1.2 Microbiological: non-sterility</i>
	<i>2.1.3 Chemical/Physical</i>
	<i>2.1.4 Biological</i>
<b>2.2</b>	<b>Batch certification of imported medicinal products</b>
	<p><i>2.2.1 Sterile Products</i></p> <p>2.2.1.1 Aseptically prepared</p> <p>2.2.1.2 Terminally sterilised</p>
	<i>2.2.2 Non-sterile products</i>

	<p>2.2.3 <i>Biological medicinal products</i></p> <p>2.2.3.1 Blood products</p> <p>2.2.3.2 Immunological products</p> <p>2.2.3.3 Cell therapy products</p> <p>2.2.3.4 Gene therapy products</p> <p>2.2.3.5 Biotechnology products</p> <p>2.2.3.6 Human or animal extracted products</p> <p>2.2.3.7 Tissue engineered products</p> <p>2.2.3.8 Other &lt;free text &gt;</p>
<b>2.3</b>	<b>Other importation activities</b>
	2.3.1 <i>Site of physical importation</i>
	2.3.2 <i>Importation of intermediate which undergoes further processing</i>
	2.3.3 <i>Biological active substance</i>
	2.3.4 <i>Other &lt;free text&gt;</i>

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

<ul style="list-style-type: none"> <li><b>MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES</b></li> </ul>	
Active Substance(s):	
<b>3.1</b>	<b>Manufacture of Active Substance by Chemical Synthesis</b>
	3.1.1 <i>Manufacture of active substance intermediates</i>
	3.1.2 <i>Manufacture of crude active substance</i>
	3.1.3 <i>Salt formation / Purification steps : &lt;free text&gt; (e.g. crystallisation)</i>
	3.1.4 <i>Other &lt;free text&gt;</i>
<b>3.2</b>	<b>Extraction of Active Substance from Natural Sources</b>
	3.2.1 <i>Extraction of substance from plant source</i>
	3.2.2 <i>Extraction of substance from animal source</i>
	3.2.3 <i>Extraction of substance from human source</i>
	3.2.4 <i>Extraction of substance from mineral source</i>
	3.2.5 <i>Modification of extracted substance &lt;specify source 1,2,3,4&gt;</i>
	3.2.6 <i>Purification of extracted substance &lt;specify source 1,2,3,4&gt;</i>
	3.2.7 <i>Other &lt;free text&gt;</i>
<b>3.3</b>	<b>Manufacture of Active Substance using Biological Processes</b>
	3.3.1 <i>Fermentation</i>
	3.3.2 <i>Cell Culture &lt;specify cell type&gt; (e.g. mammalian / bacterial)</i>

	3.3.3 <i>Isolation / Purification</i>
	3.3.4 <i>Modification</i>
	3.3.5 <i>Other &lt;free text&gt;</i>
<b>3.4</b>	<b>Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)</b>
	3.4.1 <i>Aseptically prepared</i>
	3.4.2 <i>Terminally sterilised</i>
<b>3.5</b>	<b>General Finishing Steps</b>
	3.5.1 <i>Physical processing steps &lt; specify &gt; (e.g. drying, milling / micronisation, sieving)</i>
	3.5.2 <i>Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</i>
	3.5.3 <i>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)</i>
	3.5.4 <i>Other &lt;free text&gt; (for operations not described above)</i>
<b>3.6</b>	<b>Quality control testing</b>
	3.6.1 <i>Physical / Chemical testing</i>
	3.6.2 <i>Microbiological testing (excluding sterility testing)</i>
	3.6.3 <i>Microbiological testing (including sterility testing)</i>
	3.6.4 <i>Biological testing</i>

## Part 3

1. Nature of non-compliance (check all relevant boxes)	
<input type="checkbox"/> Analytical validation	<input type="checkbox"/> Housekeeping - cleanliness, tidiness
<input type="checkbox"/> Batch release procedures	<input type="checkbox"/> In-process controls - control and monitoring of production operations
<input type="checkbox"/> Calibration of measuring and test equipment	<input type="checkbox"/> Intermediate and bulk product testing
<input type="checkbox"/> Calibration of reference materials and reagents	<input type="checkbox"/> Investigation of anomalies
<input type="checkbox"/> Cleaning validation	<input type="checkbox"/> Line clearance, segregation and potential for mix-up
<input type="checkbox"/> Complaints and product recall	<input type="checkbox"/> Personnel issues: Duties of key personnel
<input type="checkbox"/> Computerised systems - documentation and control	<input type="checkbox"/> Personnel issues: Hygiene/Clothing
<input type="checkbox"/> Computerised systems - validation	<input type="checkbox"/> Personnel issues: Training
<input type="checkbox"/> Contamination, chemical/physical - potential for	<input type="checkbox"/> Process validation
<input type="checkbox"/> Contamination, microbiological - potential for	<input type="checkbox"/> Production planning and scheduling
<input type="checkbox"/> Design and maintenance of equipment	<input type="checkbox"/> Regulatory issues: Non-compliance with manufacturing authorisation
<input type="checkbox"/> Design and maintenance of premises	<input type="checkbox"/> Regulatory issues: Non-compliance with marketing authorisation
<input type="checkbox"/> Documentation - manufacturing	<input type="checkbox"/> Regulatory issues: Unauthorised activities
<input type="checkbox"/> Documentation - quality system elements/procedures	<input type="checkbox"/> Sampling - procedures and facilities
<input type="checkbox"/> Documentation - specification and testing	<input type="checkbox"/> Self-inspection
<input type="checkbox"/> Environmental control	<input type="checkbox"/> Starting material and packaging component testing
<input type="checkbox"/> Environmental monitoring	<input type="checkbox"/> Status labelling - work in progress, facilities and equipment
<input type="checkbox"/> Equipment qualification	<input type="checkbox"/> Sterility Assurance
<input type="checkbox"/> Finished product testing	<input type="checkbox"/> Supplier and contractor audit and technical agreements
<input type="checkbox"/> Handling and control of packaging components	<input type="checkbox"/> Warehousing and distribution activities

2. Action taken/proposed\* by the third country authority or International organisation:

<input type="checkbox"/> Suspension, variation, revocation* of the manufacturing site approval in full or in part <input type="checkbox"/> Withdrawal, of current valid GMP certificate / statement <input type="checkbox"/> <b>Suspension, Revocation or Requested Variation*</b> of product registrations <input type="checkbox"/> Recall of batches already released <input type="checkbox"/> Prohibition of supply <input type="checkbox"/> Suspension of clinical trials <input type="checkbox"/> Others <free text >
3. Additional comments

Teleconference Date		Teleconference Time (GMT)		Dial in no.	
<b>EU Products manufactured at site, if known</b>	<b>Product</b>	<b>Dosage Form</b>	<b>Reference Member State, National or EMA</b>		
Human medicinal product(s)					
Veterinary medicinal product(s)					
Investigational medicinal product(s)	<b>EudraCT nos.</b>				

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

# Union format for a wholesale distribution authorisation (medicinal products for human use)

## Table of contents:

1. Union format for a wholesale distribution authorisation (medicinal products for human use)

<b>Title</b>	<b>Union format for a wholesale distribution authorisation (medicinal products for human use)</b>
Date of adoption	May 2012
Date of entry into force	By 2 January 2013
Supersedes	New
Reason for revision	
Notes	<i>To be updated with the next revision</i>

# UNION FORMAT FOR A WHOLESALER 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:

<p><b>1. MEDICINAL PRODUCTS</b></p> <ul style="list-style-type: none"><li>- <input type="checkbox"/> with a Marketing Authorisation in EEA country(s)</li><li>- <input type="checkbox"/> without a Marketing Authorisation in the EEA and intended for EEA market*</li><li>- <input type="checkbox"/> without a Marketing Authorisation in the EEA and intended for exportation</li></ul>
<p><b>2. AUTHORISED WHOLESALE DISTRIBUTION OPERATIONS</b></p> <p><b>2.1.</b> <input type="checkbox"/> Procurement</p> <p><b>2.2.</b> <input type="checkbox"/> Holding</p> <p><b>2.3.</b> <input type="checkbox"/> Supply</p> <p><b>2.4.</b> <input type="checkbox"/> Export</p> <p><b>2.5.</b> <input type="checkbox"/> Other activities(s): (please specify)</p>
<p><b>3. MEDICINAL PRODUCTS WITH ADDITIONAL REQUIREMENTS</b></p> <p><b>3.1.</b> <input type="checkbox"/> Products according to Art. 83 of 2001/83/EC<sup>1</sup></p> <ul style="list-style-type: none"><li><b>5.1.1</b> <input type="checkbox"/> Narcotic or psychotropic products</li><li><b>5.1.2</b> <input type="checkbox"/> Medicinal products derived from blood</li><li><b>5.1.3</b> <input type="checkbox"/> Immunological medicinal products</li><li><b>5.1.4</b> <input type="checkbox"/> Radiopharmaceuticals (including radionuclide kits)</li></ul> <p><b>3.2.</b> <input type="checkbox"/> Medicinal gases</p> <p><b>3.3.</b> <input type="checkbox"/> Cold chain products (requiring low temperature handling)</p> <p><b>3.4.</b> <input type="checkbox"/> Other products: (please specify here or make a reference to Annex 5)</p>

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

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<sup>1</sup> 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 .....

**ANNEX 3 (Optional)**

Name(s) of responsible person(s) .....

**ANNEX 4 (Optional)**

Date of Inspection on which dd/mm/yyyy  
authorisation was granted .....

**ANNEX 5 (Optional)**

Additional provisions based on .....  
national requirements

# Union format for a good distribution practice certificate

## Table of contents:

1. Union format for a good distribution practice certificate

<b>Title</b>	<b>Union format for a GDP certificate</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

(LETTERHEAD OF COMPETENT AUTHORITY)

Certificate No: \_\_\_/\_\_\_/\_\_\_ / Page No \_\_\_

## CERTIFICATE OF GDP COMPLIANCE OF A WHOLESALE DISTRIBUTOR

**Issued following an inspection in accordance with Art. 111 of Directive 2001/83/EC and/or <National Legal basis/statement from authority>**

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

The wholesale distributor.....  
Distributor's alternative name.....  
Site address.....  
Additional details on units inspected.....

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:  
.....  
.....

and/ or

Has been inspected under the national inspection programme in connection with authorisation number ..... in accordance with <National legal basis/statement from authority>

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 and/or in Article 99(6) of Regulation (EU) 2019/6.

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 EudraGMDP. 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]<sup>1</sup>

.....

.....

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

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

# Union format for a good distribution practice certificate for active substances to be used as starting materials in medicinal products

## Table of contents:

1. Union format for a good distribution practice certificate for active substances to be used as starting materials in medicinal products

<b>Title</b>	<b>Union format for a GDP certificate for active substances to be used as starting materials in medicinal products</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

# CERTIFICATE OF GDP COMPLIANCE OF A DISTRIBUTOR OF ACTIVE SUBSTANCES FOR USE AS STARTING MATERIALS IN MEDICINAL PRODUCTS

**Issued following an inspection in accordance with Art. 111 of Directive 2001/83/EC and/or <National legal basis/statement from authority>**

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

The active substance distributor.....

Distributor's alternative name: .....

Site address .....

Additional details on units inspected:

.....

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\*.....

and/ or

has been inspected under the national inspection programme in connection with registration number ..... in accordance with <National legal basis/statement from authority>

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 and/ or Article 95(8) of Regulation (EU) 2019/6.

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 EudraGMDP. 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]<sup>1</sup>

.....

.....

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

**\*Delete where not applicable**

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

# GDP inspection report – Union format

## Table of contents:

1. GMP inspection report - Union format
2. Definition of significant deficiencies

<b>Title</b>	<b>GDP inspection report</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable



## GDP Inspection Report – Union Format

<b>1. Report Reference no.:</b>	
<b>2. Inspected site(s):</b>	
Name and full address of the inspected site.	
<b>3. Authorised operations:</b>	
<input type="checkbox"/> Procurement <input type="checkbox"/> Holding <input type="checkbox"/> Supply <input type="checkbox"/> Export <input type="checkbox"/> Brokering <input type="checkbox"/> Other activities: (please specify)	
<b>4. Inspection date(s):</b>	Day(s), month, year.
<b>5. Inspector(s):</b>	
Name(s) of the inspector(s).	
Name(s) of the Competent Authority(ies).	
<b>6. References:</b>	Wholesale Distribution Authorisation Number or Registration Number of Broker
<b>7. Introduction:</b>	

Summarise business activities of company and product categories handled.

Date of previous inspection.

Name(s) of Inspector(s) involved in previous inspection.

Major changes since the previous inspection.

Cover main personnel, premises, equipment and facility changes.

If available, refer to or incorporate company documents describing changes and future plans

The majority of report text should be in past tense, as report relates to what was observed on day(s) of inspection.

Future plans may be written in different tense.

#### **8. Scope of Inspection:**

The scope of the inspection should include a short description of the inspection (e.g. continued compliance of the distribution operation with Guidelines on GDP).

The reason for the inspection should be specified (routine GDP inspection, application for new authorisation, inspection for cause).

Set out objective(s) of inspection clearly.

#### **9. Inspected activities:**

Each activity inspected should be specified.

#### **10. Activities not inspected:**

Where necessary attention should be drawn to areas or activities not inspected on this occasion.

#### **11. Personnel met during the inspection:**

The names and titles of key personnel met should be specified.

#### **12. Inspectors' findings and observations relevant to the inspection and deficiencies:**

This section should include reference to relevant headings of the Guidelines on GDP.

A brief overview of the operation should be provided in the context of the heading.

Procedures or aspects of note may be documented. Future proposals that may impact on the next inspection may also be documented.

This section should, where appropriate, link the findings of the inspection to the deficiencies and be used to explain classification.

- a. Overview of inspection findings from last inspection and the corrective action taken.
- b. Quality Management
- c. Personnel
- d. Premises and Equipment
- e. Documentation
- f. Operations
- g. Complaints, Returns, Suspected Falsified Medicinal Products and Recalls
- h. Outsourced Activities
- i. Self-Inspection
- j. Transportation
- k. Specific Provisions for Brokers

**13. Other specific issues identified:**

e.g. Relevant future changes announced by company

**14. Miscellaneous:**

e.g. Samples taken

**15. Annexes attached:**

List of any annexes attached

**16. List of Deficiencies classified into critical, major and others:**

All deficiencies should be listed in accordance with the appropriate heading from the Guidelines on GDP.

All deficiencies should be referenced and linked to a paragraph or paragraphs within the Guidelines on GDP.

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

The company should be asked to inform the Competent Authority about the proposed time schedule for corrections.

Each deficiency should, if at all possible, be stated as a negative.

The deficiency should be clear, e.g. 'the approach to temperature monitoring was not GDP compliant' versus 'the approach to temperature monitoring was not GDP compliant in that:

- Temperature probes had not been calibrated
- Temperature records were not reviewed regularly.'

Words/phrases such as "insufficient" and "appeared to be" should be avoided, if possible. Words such as "inadequate", "non-compliant" or "deficient" should be used in qualifying the deficiency.

For classification of deficiencies see last page.

#### **17. Inspectors' Comments (optional):**

Could be used to capture factual information and verbal undertakings given during the inspection or comment on the responses of the company.

#### **18. Recommendations (optional):**

List recommendations to either the company or authorities, if any.

#### **19. Summary and conclusions:**

The Inspector(s) should state whether, within the scope of the inspection, the company operates in accordance with the Commission Guidelines on GDP of Medicinal Products for human use\* or GDP for veterinary medicinal products\*\*, where relevant, that appropriate corrective actions are implemented and mention any other item to alert requesting authority. Reference may be made to conclusions recorded in other documents, such as the close-out letter, depending on national procedures.

\*Directive 2001/83/EC Art 84 /\*\*Regulation (EU) 2019/6 Art. 99(6)

#### **20. The inspection report should be signed and dated by the inspector(s) having participated in the inspection.**

**Name(s):**

**Signatures(s):**

**Organisation(s):**

**Date:**

Distribution of Report:

## **Annex**

### **Definition of Significant GDP Deficiencies**

#### **1. Critical Deficiency:**

Any departure from Guidelines on Good Distribution Practice resulting in a medicinal product causing a significant risk to the patient/animal and public or animal health. This includes an activity increasing the risk of falsified medicines reaching the patients/animal.

A combination of a number of major deficiencies that indicates a serious systems failure.

An example of a critical deficiency could be:

Purchase from or supply of medicinal products to a non-authorized person;

Storage of products requiring refrigeration at ambient temperatures;

Rejected or recalled products found in sellable stock.

#### **2. Major Deficiency:**

A non-critical deficiency:

which indicates a major deviation from Good Distribution Practice;

or which has caused or may cause a medicinal product not to comply with its marketing authorisation in particular its storage and transport conditions;

or which indicates a major deviation from the terms and provisions of the wholesale distribution authorisation;

or a combination of several other deficiencies, none of which on their own may be major, but which may together represent a major deficiency.

#### **3. Other Deficiency:**

A deficiency which cannot be classified as either critical or major, but which indicates a departure from Guidelines on Good Distribution Practice.

# Statement of non-compliance with good distribution practice

## Table of contents:

1. Union format for a statement of non-compliance with good distribution practice

<b>Title</b>	<b>Statement of non-compliance with good distribution practice</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable

(LETTERHEAD OF COMPETENT AUTHORITY)

Report No: \_\_ \_ / \_\_ \_ / \_\_ \_ / \_\_ \_

## STATEMENT OF NON-COMPLIANCE WITH GDP

**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 and/or <National legal basis/statement from authority>.

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

The wholesale distributor.....

Distributor's alternative name: .....

Authorisation number.....

Site address.....

Additional details on units inspected: .....

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 and/or Article 99(6) of Regulation (EU) 2019/6.



**Part 2**

Wholesale distribution activity affected: <free text>
---

**Part 3**

- |   |
|---|
| <ul style="list-style-type: none"><li>• Nature of non-compliance: &lt;free text&gt;</li></ul>         |
| <ul style="list-style-type: none"><li>• Action taken/proposed by the NCA: &lt;free text&gt;</li></ul> |
| <ul style="list-style-type: none"><li>• Additional comments: &lt;free text&gt;</li></ul>              |

Teleconference Date:	Teleconference Time (CET):	Dial in no.:
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...../...../..... [date]

Name and signature of the authorised person of the Competent Authority of [country]<sup>1</sup>

.....  
.....

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

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<sup>1</sup> The signature, date and contact details should appear on each page of the statement.

# Statement of non-compliance with good distribution practice of a distributor of active substances for use as starting materials in medicinal products

## Table of contents:

1. Union format for a statement of non-compliance with good distribution practice of a distributor of active substances for use as starting materials in medicinal products

<b>Title</b>	<b>Statement of non-compliance with good distribution practice of a distributor of active substances for use as starting materials in medicinal products</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in May 2012
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
Notes	Not applicable

**STATEMENT OF NON-COMPLIANCE WITH GDP OF A DISTRIBUTOR OF ACTIVE SUBSTANCES FOR USE AS STARTING MATERIALS IN MEDICINAL PRODUCTS**

**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 and/or <National legal basis/statement from Authority>.

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

The active substance distributor.....

Distributor's alternative name: .....

Site address: .....

Additional details on units inspected: .....

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 and/or in Article 95(8) of Regulation (EU) 2019/6.

**Part 2**

<input type="checkbox"/> All registered active substances distributed are affected
<input type="checkbox"/> Specify which Active Substances are affected: <free text>

**Part 3**

<ul style="list-style-type: none"><li>• Nature of non-compliance: &lt;free text&gt;</li></ul>
<ul style="list-style-type: none"><li>• Action taken/proposed by the NCA: &lt;free text&gt;</li></ul>
<ul style="list-style-type: none"><li>• Additional comments: &lt;free text&gt;</li></ul>

Teleconference Date:	Teleconference Time (CET):	Dial in no.:
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.../.../... [date]

Name and signature of the authorised person of the Competent Authority of [country]<sup>1</sup>

.....

.....

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

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<sup>1</sup> The signature, date and contact details should appear on each page of this statement.

# Request form for the exchange of information on marketing authorisation holders or manufacturing authorisation holders between the competent authorities in the EEA

## Table of contents:

1. Union format for a request form for the exchange of information on marketing authorisation holders or manufacturing authorisation holders between the competent authorities in the EEA

<b>Title</b>	<b>Request form for the exchange of information on marketing authorisation holders or manufacturing authorisation holders between the competent authorities in the EEA</b>
Date of adoption	May 2012
Date of entry into force	By 2 January 2013
Supersedes	New
Reason for revision	New
Notes	Not applicable

## 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. EudraGMDP) for the exchange of information

Reference no.:	No. of pages/No. of attachments:	Date:
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### Requesting Competent Authority

Competent Authority/ Country	
Address/phone/fax	
Contact Person	
Email of Contact Person	

### Recipient Competent Authority

Competent Authority/ Country	
Address/phone/fax	
Contact Person	
Email of Contact Person	

### Request for Exchange of Information on *[complete as appropriate]*

MAH - Address/phone/fax/Email	
QPPV/ PSMF site – Address/phone	
Medicinal Product/dosage form/strength/INN/MA	
Manufacturer - Address/phone/fax/Email	
Information requested	

# 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.....

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

Name and signature of a responsible officer of the reporting competent authority:

.....Date:.....

# Union format for registration of manufacturer, importer or distributor of active substance

## Table of contents:

1. Union format for registration of manufacturer, importer or distributor for active substance

<b>Title</b>	<b>Union format for registration of manufacturer, importer or distributor for active substance</b>
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version published in April 2022
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	Not applicable



<Letterhead of Validating Authority>

## **Union format for registration<sup>1</sup> of manufacturer, importer or distributor of active substances**

- Registration number
  
- Name or corporate name of registrant
- 2.a Alternative name of authorisation holder
- Permanent or Legal address of registrant
- 3.a Additional details on units inspected of registrant's legal address
- Address(es) of site(s) where registered activities take place  
(All relevant sites should be listed if not covered by separate registrations)
- 4.a Additional details on units inspected of site(s) address(es)
- National legal basis of registration
  
- Name of responsible officer of the competent authority of the member state validating the registration<sup>2</sup>
  
- Signature<sup>2</sup>
  
- 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.

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<sup>1</sup> Without prejudice to any further national legislative requirements

<sup>2</sup> Optional

## SCOPE OF REGISTRATION

Name and address of the site:

Human Medicinal Products

Veterinary Medicinal Products

<b>1. MANUFACTURING OPERATIONS</b>	
Active Substance(s): (H/V/ H + V)	
<b>A.</b>	<b>Manufacture of Active Substance by Chemical Synthesis</b>
	<ol style="list-style-type: none"><li>1. <i>Manufacture of active substance intermediates</i></li><li>2. <i>Manufacture of crude active substance</i></li><li>3. <i>Salt formation / Purification steps : &lt;free text&gt; (e.g. crystallisation)</i></li><li>4. <i>Other &lt;free text&gt;</i></li></ol>
<b>B.</b>	<b>Extraction of Active Substance from Natural Sources</b>
	<ol style="list-style-type: none"><li>1. <i>Extraction of substance from plant source</i></li><li>2. <i>Extraction of substance from animal source</i></li><li>3. <i>Extraction of substance from human source</i></li><li>4. <i>Extraction of substance from mineral source</i></li><li>5. <i>Modification of extracted substance &lt;specify source 1,2,3,4&gt;</i></li><li>6. <i>Purification of extracted substance &lt;specify source 1,2,3,4 &gt;</i></li><li>7. <i>Other &lt;free text&gt;</i></li></ol>
<b>C.</b>	<b>Manufacture of Active Substance using Biological Processes</b>
	<ol style="list-style-type: none"><li>1. <i>Fermentation</i></li><li>2. <i>Cell Culture &lt;specify cell type&gt; (e.g. mammalian / bacterial )</i></li><li>3. <i>Isolation / Purification</i></li><li>4. <i>Modification</i></li><li>5. <i>Other &lt;free text&gt;</i></li></ol>
<b>D.</b>	<b>Manufacture of sterile active substance (note Parts A, B &amp; C, to be completed as applicable)</b>
	<ol style="list-style-type: none"><li>1. <i>Aseptically prepared</i></li><li>2. <i>Terminally sterilised</i></li></ol>
<b>E.</b>	<b>General Finishing Steps</b>
	<ol style="list-style-type: none"><li>1. <i>Physical processing steps &lt; specify &gt; (e.g. drying, milling / micronisation, sieving)</i></li></ol>

	<ol style="list-style-type: none"> <li>2. <i>Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</i></li> <li>3. <i>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)</i></li> <li>4. <i>Other &lt;free text&gt; (for operations not described above)</i></li> </ol>
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Registration No:  
Page # of #

<b>F.</b>	<p><b>Quality Control Testing</b></p> <p><i>This section should be completed only if any parts of sections A, B, C, D, E are completed</i></p>
	<ol style="list-style-type: none"> <li>1. <i>Physical / Chemical testing</i></li> <li>2. <i>Microbiological testing (excluding sterility testing)</i></li> <li>3. <i>Microbiological testing (including sterility testing)</i></li> <li>4. <i>Biological Testing</i></li> </ol>

<b>2. IMPORTATION AND DISTRIBUTION OPERATIONS</b>		
<b>A.</b>	<p><b>Importation</b></p> <p><i>(list all imported active substances together with details of the relevant manufacturers, and where applicable, distributors)</i></p>	
	<i>Active substance</i>	<i>3rd country manufacturer (name &amp; address)</i>
		<i>Distributor (name &amp; address)</i>
<b>B.</b>	<b>Distribution</b>	
	<i>Active substance(s) (list all active substances for which distribution operations apply)</i>	

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<sup>1</sup>

Signature

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<sup>1</sup> Optional

## History of changes to the Compilation of Procedures

Date	Details
December 2003	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.
February 2004 (rev. 1)	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.
September 2004 (rev. 2)	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 Union.
February 2005 (rev. 3)	Revision to procedure on verification of GMP in third countries.
September 2005 (rev. 4)	<p>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 Union formats for a GMP inspection report and manufacturing authorisation and a Union format for a GMP certificate were introduced.</p> <p>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.</p> <p>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.</p> <p>The title of the procedure for handling suspected quality defects was corrected.</p>
July 2006 (rev. 5)	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.

September 2006 (rev. 5 reformatted)	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.
October 2006 (rev. 6)	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.
March 2007 (rev. 7)	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.
April 2008 (rev 8)	The Quality System Framework for GMP Inspectorates was revised to introduce a quality risk management approach following the implementation of ICH Q9 guideline.
August 2008 (rev. 9)	Update to Training and Qualifications of GMP Inspectors document.
March 2010 (rev. 10)	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.
August 2010 (rev. 11)	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 Union 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 Union inspection report format in March 2010.
January 2011 (rev. 12)	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.
July 2011 (rev. 13)	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)
May 2012 (rev. 14)	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.
July 2012 (rev. 15)	The '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'.
June 2013 (rev. 16)	<p>New documents added under the 'Procedures Related to GDP Inspections' section: GDP Inspection Procedure- Medicinal Products for Human Use, The Issue and Update of GDP Certificates- Medicinal Products for Human Use.</p> <p>A new section 'Interpretation Documents' has been created and an interpretation document for the Union format of a manufacturing/importation authorisation' has been included.</p> <p>The procedure 'A Model for Risk Based Inspection Planning of Pharmaceutical Manufacturers' (in the section 'Procedures Related to GDP Inspections') has been revised to incorporate the PI-037-1-PIC/S Recommended Model for Risk-based Inspection Planning in the GMP Environment.</p> <p>In the section 'Forms used by regulators', the template for 'GDP Inspection Format' has been added.</p>
October 2014 (rev. 17)	<p>The "Procedure for dealing with serious GMP non-compliance thus requiring co-ordinated measures to protect public or animal health" has replaced the "Procedure for Dealing with Serious GMP Non-compliance or</p> <p>Voiding/ Suspension of CEPs Thus Requiring Co-ordinated Administrative</p>

	<p>Action". The new procedure reflects the experience gained with the superseded procedure.</p> <p>The "Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials" has been revised in order for it to be aligned with new requirements for medicinal products</p> <p>Compilation of Union Procedures on Inspections and Exchange of Information</p> <p>EMA/572454/2014 Page 253/253</p> <p>for human use introduced by Directive 2011/62/EU.</p>
<p>July 2021 (rev. 18)</p>	<p>The Compilation has been restructured and split into two parts, Part I and Part II. Documents in Part I are Compilation procedures whereas Part II includes interpretation documents together with templates. The Introduction has been revised accordingly to reflect this change.</p> <p>Furthermore, spelling and punctuation mistakes have been corrected throughout the whole document as well as some updates of terminology.</p> <p>In addition, the following documents have been revised:</p> <ul style="list-style-type: none"> <li>• Management of Reports of Suspected Quality Defects in Medicinal Products - The procedure was revised in order to provide more comprehensive guidance following quality risk management principles</li> <li>• Management of Rapid Alerts Arising from Quality Defects Risk Assessment - The procedure was revised in order to provide more comprehensive guidance following quality risk management principles</li> <li>• Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health -Procedure has been revised as a result of experience with the superseded procedure; Appendix 6: Supervisory Risk Assessment has been updated.</li> <li>• Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries</li> <li>• A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers</li> <li>• Interpretation of the Union format for GMP certificate</li> </ul>



	<ul style="list-style-type: none"> <li>• Interpretation of the Union format for a wholesale distribution authorisation (medicinal products for human use) – new procedure</li> <li>• Union Format for a GMP Certificate</li> <li>• The issue and update of GMP certificates- minor update has been made primarily to align the procedure with experience.</li> <li>• Serious GMP Non-Compliance Info-from Third Countries or International Organisations</li> <li>• STATEMENT OF NON-COMPLIANCE WITH GMP Interpretation of the Union Format for Manufacturer/Importer Authorisation</li> <li>• Procedure for compliance management – new procedure</li> </ul>
April 2022 (Rev 18 corrigendum)	a corrigendum of revision 18 of the Compilation of Union Procedures on Inspections and Exchange of Information (CoUP) to include 4 updated legal references which were overlooked with the publication of revision 18 of the CoUP
June 2023 (Rev 19)	Modifications were introduced through the revision 19 as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. A new procedure was added: EU/EEA Programme for Maintenance of Equivalence in Supervision of Good Manufacturing Practice (GMP) Compliance of Pharmaceutical Companies. A revision of the Union format for a wholesale distribution authorisation and interpretation document will be included in the upcoming revision.
September 2023 (Rev 19.1)	Minor modifications introduced to remove mention of repealed Directive 2003/94/EC and further minor editorial changes were introduced.