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Conduct of inspections of pharmaceutical manufacturers or importers

Table of contents:

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Conduct of inspections of pharmaceutical manufacturers or importers

1. Introduction

In line with Articles 42 and 111 of Directive 2001/83/EC and 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[1].

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.

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

[1] 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.

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.