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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

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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[1]

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 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

[1] 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.

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 actives 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 actives 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 3rd 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.

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