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Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials

Introduction

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

The relevant sections from the amended Directives 2001/83/EC and 2001/82/EC are set out in Annex 1.

Purpose

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

Scope

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

NOTES:
(i) As the characterisation and quality of most biological substances is highly dependent on the production process, their manufacture is generally considered to be an integral part of the manufacturing process for the dosage form and subject to routine inspection, and so therefore lies outside the scope of this guideline.

(ii) Similarly, in the case of aseptically produced medicinal products, the sterilisation and subsequent aseptic handling of the active substance is considered to be part of the manufacturing process for the dosage form and is subject to routine inspection, so lies outside the scope of this guideline.

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Principle

A Competent Authority must be able to satisfy itself that the manufacture and distribution of active substances has been carried out in accordance with the principles of good manufacturing practice for active substances used as starting materials. Where it has grounds for suspecting non-compliance, the Competent Authority may carry out announced or unannounced inspections at the company concerned.

Article 46(f) of Directive 2001/83/EC and Article 50(f) of Directive 2001/82/EC oblige the holder of a manufacturing authorisation to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

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

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

Examples of when Inspection may be appropriate

The following is a list of examples of when the inspection of premises used to manufacture a starting material, which is, in turn, used in the manufacture of a human or veterinary medicinal product, may be required;

1. Directly linked to EU Legislation

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

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

1.3 When requested by the European Commission where the Commission provides a written request detailing why an inspection is necessary (Article 111(1))/Article 80 (1)

1.4 When requested by the European Medicines Agency (EMEA) in relation to the assessment of a product under the centralised system or in connection with matters

referred to it in accordance with Community legislation (Article 111(1)/ Article 80 (1))

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

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

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

1.8 Where there is disagreement between Member States on the conclusions from an inspection (Article 122(3)/ Article 90).

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

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

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

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

2. Other Examples

2.1 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.

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

2.3 On receipt of information from another Competent Authority, based inside or outside the EEA, or other plausible information, that activities at the premises

are not compliant with the GMP principles. This may include premises located inside or outside the EEA. It may also include invocation of the safeguard clause contained in a MRA where the competent authority considers that it is imperative that an inspection of an active substance manufacturer located in the territory of an MRA partner be carried out.

2.4 Where there are suspicions regarding the authenticity of data, relating to an active substance, which have been submitted in support of a marketing authorisation application.

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

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

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

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

References

Directive 2001/82/EC as amended by Directive 2004/28/EC

Directive 2001/83/EC as amended by Directives 2002/98/EC, 2004/24/EC and 2004/28/EC

ANNEX 1

Relevant articles from Directives 2001/82/EC (as amended by Directive 2004/28/EC) and 2001/83/EC (as amended by Directives 2002/98/EC, 2004/24/EC and 2004/28/EC)

The sections from Directives 2001/83/EC and 2001/82/EC, as amended, which are relevant to inspections of manufacturers of active substances used as starting materials are:

Article 19.1 of Directive 2001/83/EC

In order to examine the application submitted in accordance with Articles 8, 10, 10a, 10b and 10c, the competent authority of the Member State

1. must verify whether the particulars submitted in support of the application comply with the said Articles 8, 10, 10a, 10b and 10c and examine whether the conditions for issuing an authorisation to place medicinal products on the market (marketing authorisation) are complied with.

Article 23(1) of Directive 2001/82/EC.

In order to examine the application submitted pursuant to Articles 12 to 13d, Member States' competent authorities:
1) Shall check that the documentation submitted in support of the application complies with Articles 12 to 13d and ascertain whether the conditions for the issue of the marketing authorisation have been fulfilled.

Article 46(f)/(Article 50 (f)

The holder of a manufacturing authorisation shall be at least obliged to:
(f) Use, as starting materials, only active substances which have been manufactured in accordance with the detailed guidelines on Good Manufacturing Practice.

Article 46a/Article 50a
"For the purposes of this Directive, manufacture of active substances used as stating materials shall include both total and partial manufacture and import of an active substance uses as a starting material as defined in Part 1, point 3.2.1.1 (b) Annex 1, and the various processes of dividing up, packaging or presentation prior to its incorporation into a (veterinary) medicinal product, including repackaging or relabelling, such as are carried out by a distributor of starting materials."

Article 47/Article 51

"The principles of good manufacturing practice for active substances used as starting materials referred to in point (F) of Article 46/Article 50 shall be adopted in the form of detailed guidelines."

Article 111(1)/Article 80 (1)

“The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials --------- whenever it considers that there are grounds for suspecting non compliance with the principles and guidelines of good manufacturing practice referred to in Article 47/Article 51.

In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body ------ (European Directorate for the Quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.

The competent authority of the Member State concerned may carry out inspections of starting material manufacturers at the specific request of the manufacturer himself.

Such inspections shall be carried out by officials representing the competent authority who shall be empowered to:

a) Inspect the manufacturing or commercial establishment of manufacturers ------ -- of active substances (and certain excipients) used as starting materials, ------

b) Take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a Laboratory designated for that purpose by a Member State,

c) Examine any documents relating to the object of the inspection -------- "

Article III (3) / Article 80(3)

After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good manufacturing practice laid down in Article 47/Article 51 --------- . The contents of such reports shall be communicated to the manufacturer --------- who has undergone the inspection”.

Article 111(4)/Article 80 (4)

“Without prejudice to any arrangements which may have been concluded between the Community and Third Countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1”i.e (Article 111(1)/Article 80 (1))

Article 111(5)/Article 80 (5)

“----------. If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up”.

Article 122(1)/Article 90

“Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the certificate referred to in Article 111(5)/Article 80 (5) ----- are fulfilled”. (Wording of Article 90 of 2001/82/EC differs slightly)

Article 122(2)/Article 90

“Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111 (3)/Article 80 (3) to the competent authorities of another Member State.”

Article 122(3)/Article 90

The conclusions reached in accordance with Article 111(1) shall be valid throughout the Community. However, in exceptional cases, if a Member State is unable, for reasons relating to public (or animal) health, to accept conclusions reached following an inspection under Article 111(1)/ Article 80 (1), that Member State shall forthwith inform the Commission and the Agency. The Agency shall inform the Member States concerned.

When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States who are not parties to the disagreement.” (Wording of Article 90 of 2001/82/EC differs slightly)