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The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 21: Importation of medicinal products

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: New annex.

Reasons for changes: Not applicable at this occasion. It is a new annex.

Deadline for coming into operation: to be determined.

1. Scope

1.1. This Annex summarizes the GMP requirements applicable to a Manufacturing Import Authorisation (MIA) holder which imports medicinal products (human and veterinary) from outside the EU/EEA. The guidance in the main chapters and annexes of the EU GMP also apply, as appropriate for the activities carried out, and should be consulted for more detailed guidance.

Medicinal products which enter EU/EEA with the intention of export only and which are not processed nor released for placing on the EU/EEA market, are not covered by this Annex.

2. Principles

2.1. For the purpose of this annex, the term importation refers to the action of physically bringing medicinal product, from outside the territory of EEA/EU what implies the necessity of clearing it into the customs territory of an EU/EEA state QP certification of a batch of medicinal product takes place after physical importation and custom clearance. Imported dosage forms and intermediates may undergo further manufacturing operations in accordance with the marketing authorisation, prior to QP certification or confirmation, as appropriate. The sites which are considered to have specific importation responsibilities in relation to a medicinal product or imported dosage form are:

a) Site of Physical Importation.
b) Site of QP certification of imported medicinal products or QP confirmation for intermediate products undergoing further processing, as appropriate.

The above importation responsibilities must be carried out by entities appropriately authorized under a MIA.

2.2. All stages of manufacture of imported medicinal products which are carried out in third countries should be conducted in accordance with EU GMP or equivalent standards and in conformance with the Marketing Authorisation (MA), the clinical trial authorization (CTA) and the relevant quality agreement, as applicable.

2.3. For products authorized in the EU/EEA, the overall responsibility for placing the medicinal products on the market lies with the marketing authorization holder (MAH).

2.4. The Qualified Person certifying the batch has to ensure that all the medicinal products for human or veterinary use that are imported into the Union from a third country were manufactured in accordance with EU GMP or equivalent standard and tested in the Union, unless there are appropriate arrangement in place between the Union and the third country (e.g. Mutual Recognition Agreement or ACAA). See also Annex 16 for further guidance.

2.5. Testing in an EU/EEA state covers all the tests needed to demonstrate that the medicinal product meets the specifications that are set out in the marketing authorization.

2.6. Written agreements should be in place between the site(s) performing manufacturing, importation activities and the MAH, as appropriate, in accordance with Chapter 7 of the EU GMP.

3. Pharmaceutical Quality System

3.1. The site(s) conducting importation activities should have an appropriately detailed documented Pharmaceutical Quality System in accordance with Chapter 1 of the EU GMP Guide and reflecting the scope of the activities carried out.

3.2. Product Quality Reviews should be performed by the site performing QP certification for the products imported, including products imported for export.

- Written agreements should be in place to define the relative responsibilities of the MAH, the importer(s) and the third country manufacturers, as appropriate, in relation to compiling of the Product Quality Reviews as outlined in Chapter 1 of the EU GMP.
- In addition to the PQR requirements described in Chapter 1, where sampling of the imported product is conducted in a third country in accordance to Annex 16, then the PQR should include assessment of the basis for continued reliance on this sampling practice. PQRs should also include a review of deviations relating to transportation. Specific requirements for sampling and transportation of imported products are detailed further in Annex 16.
- As part of this review, the analytical results from importation testing should be compared with those in the Certificate of Analysis generated by the third country manufacturer. Any trends or discrepancies should be documented and investigated.

4. Premises and equipment

4.1. The site(s) involved in importation activities should have adequate premises and equipment in order to perform their respective activities in accordance with EU GMP.

4.2. Imported medicinal products should be stored under quarantine after receipt, until their release for further processing or following QP certification or confirmation as appropriate, in accordance with Annex 16. Segregated areas should exist for quarantined products. Any system replacing the physical quarantine should give equivalent security.

5. Documentation

5.1. The MIA holder responsible for QP certification of the batch should have access to full batch documentation at all times. Other MIA holders involved in the importation process should have access to batch documentation as necessary in accordance with the activities for which the site is responsible, and as reflected in under written agreements between the parties involved in the importation process. .

5.1.1. The MIA holder responsible for QP certification should have access to those documents which would support batch certification as defined in Annex 16. The frequency at which full batch documentation is reviewed by the QP certifying the product should be justified and defined in the Pharmaceutical Quality System. Documentary evidence should be available to demonstrate that the QP has certified the batch in accordance with the MA and any other regulatory restrictions that may apply (e.g. where an EU GMP certificate restricts activities to specific manufacturing units/buildings at the third country manufacturing site).

5.1.2. The site of physical importation should have, at minimum, details of transportation and receipt of the product (see also Annex 16).

5.1.3. Relevant purchasing and delivery documentation should be available for inspection at MIA holder responsible for QP certification and clearly indicate:
- The site from which the product has been dispatched (the origin of the product).
- The site of physical importation.
- Shipping details (including, transportation route and temperature monitoring records) and customs documentation, as applicable.

5.2. Documentation must be retained in accordance with the requirements of Chapter 4 of the EU GMP Guide. The MIA holder responsible for QP certification should ensure that the third country manufacturing site has a record retention policy equivalent to EU requirements.

5.3. Batch documentation, including batch certificates, supplied by the third country manufacturing site should be in a language understood by the importer. It may be necessary to provide documents in more than one language to facilitate understanding.

5.4. There should be documentary evidence that the site performing QP certification has qualified the third country manufacturer and regularly monitors its performance by periodic on-site audits, to ensure that the imported products are manufactured in accordance with EU GMP or equivalent requirements and the MA.

5.5. Where batches have been subdivided and the individual quantities imported separately, documentation confirming reconciliation of the quantities should be made available at the site where QP certification takes place.. Any discrepancy should be investigated.

6. Operations

6.1. The manufacturing site where QP certification occurs should ensure that an ongoing stability program is in place, as required in Chapter 6. The ongoing stability program may be carried out at a third country site as an outsourced activity provided that the QP has all the necessary information to assure ongoing product quality. Details of the ongoing stability program, such as protocols, results and reports should be available for inspection at the MIA holder responsible for QP certification.

6.2. The QP certifying the batch is responsible for ensuring that, where required, the safety features have been affixed to the packaging.

6.3. The certifying QP is also responsible for ensuring that reference and retention samples have been taken in accordance with the requirements in Annex 19.

7. Complaints, Quality Defects and Product Recalls

7.1. Adequate provisions should be in place between the site(s) performing importation activities, the third country manufacturer and the MAH for handling complaints, quality defects and product recalls as required in Chapter 8 of the EU GMP Guide. This should be defined in contractual arrangements.