



Brussels, 16.2.2022  
C(2022) 843 final

## **GUIDELINES**

### **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**

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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 Regulation 2019/6 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, and the Clinical trials Regulation 536/2014, the Commission Delegated Regulation 2017/1569 supplementing it.

**Status of the document:** New annex.

**Reasons for changes:** Not applicable at this occasion.

**Deadline for coming into operation:** 21 August 2022 (6 months after publication].

## 1. Scope

This Annex summarizes the GMP requirements applicable to a Manufacturing Import Authorisation (MIA) holder, when importing medicinal products (human, investigational and veterinary) from outside the EU/EEA. The guidance in the main chapters and other annexes of the Guide to Good Manufacturing Practice for Medicinal Products ("the EU GMP Guide") also apply, as appropriate, for other GMP activities carried out and should be consulted for supplementary guidance. Medicinal products that enter the EU/EEA with the intention of export only and that are not processed in any form 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 a medicinal product, from outside the territory of EEA/EU; fiscal transactions are not part of this annex. Qualified Person (QP) certification or confirmation, as appropriate, of a batch of a medicinal product takes place only after physical importation and custom clearance into the customs territory of an EU/EEA State. Imported bulk products and intermediate products may undergo further manufacturing operations in accordance with the marketing authorisation or clinical trial 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, a bulk or an intermediate product, are:
- a) Site of Physical Importation.
  - b) Site of QP certification of imported medicinal products or QP confirmation for bulk or 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 that are carried out in third countries should be conducted in accordance with the EU GMP Guide or equivalent standards and in conformance with the Marketing Authorisation (MA), the clinical trial authorisation (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 authorisation holder (MAH).
- 2.4. The Qualified Person certifying the batch must ensure that all the medicinal products for human or veterinary use or investigational medicinal products that are imported into the Union from a third country were manufactured in accordance with the EU GMP Guide or recognised equivalent standards, and for products with a marketing authorisation, tested upon importation in the Union, unless there are appropriate arrangements in place between the Union and the third country (e.g. Mutual Recognition Agreement (MRA) or Agreement on conformity assessment and acceptance of industrial products, ACAA). See also Annex 16 of the EU GMP

Guide and Annex 13, the detailed guidelines on GMP for Investigational Medicinal Products (IMPs) for further guidance.

- 2.5. Testing in an EU/EEA state should cover all the tests needed to demonstrate that the medicinal product meets the specifications that are set out in the marketing authorisation.
- 2.6. Written agreements should be in place between the site(s) performing manufacturing, importation activities and the MAH or sponsor, as appropriate, in accordance with Chapter 7 of the EU GMP Guide.

### **3. Pharmaceutical Quality System**

- 3.1. The site(s) conducting importation activities should have an appropriately detailed 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 responsible for QP certification for the products imported, including products imported for further processing before export with the exception of investigational medicinal products.
  - Written agreements should be in place to define the respective responsibilities of the MAH, the importer(s), the site responsible for QP certification 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 Guide.
  - In addition to the Product Quality Review (PQR) requirements described in Chapter 1 of the EU GMP Guide, where sampling of the imported product is conducted in a third country in accordance with Annex 16 of the EU GMP Guide, the PQR should include an assessment of the basis for continued reliance on this sampling practice. PQRs should also include a review of deviations relating to transportation up to the point of batch certification. Specific requirements for sampling and transportation of imported products are detailed further in Annex 16 of the EU GMP Guide.
  - 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 discrepancies or out of trends (OOT) should be documented and investigated.

### **4. Premises and equipment**

- 4.1. The site(s) involved in importation activities should have adequate premises and equipment to ensure the respective activities are performed in accordance with EU GMP Guide.
- 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 of the EU GMP Guide. Segregated areas should exist for quarantined products. Any system replacing the physical quarantine should ensure an equivalent level of security.

### **5. Documentation**

- 5.1. Full batch documentation must be available to the MIA holder responsible for QP certification or confirmation of the batch, as appropriate, at the time of certification or confirmation of the batch. 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 written agreements between the parties involved in the importation process.
- 5.1.1. The site responsible for QP certification or confirmation, as appropriate, should have access to those documents that would support batch certification as defined in Annex 16 of the EU GMP Guide. The frequency at which full batch documentation is reviewed at the site responsible for QP certification or confirmation, as appropriate, of the product should be justified on a risk assessment basis and defined in the Pharmaceutical Quality System. Documentary evidence should be available to demonstrate that the QP has certified or confirmed the batch in accordance with the MA or clinical trial authorisation 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 documentation on the site of physical importation should include, at a minimum, the details of transportation and receipt of the product (see also Annex 16 of the EU GMP Guide).
- 5.1.3. Relevant ordering and delivery documentation should be available for inspection at the site responsible for QP certification or confirmation, as appropriate, and clearly indicate:
- The site from where 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, such as the packing list, freight documentation or customs import declaration, as applicable.
- 5.2. Documentation must be retained in accordance with the requirements of Chapter 4 of the EU GMP Guide. The site 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 format 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, either by the site performing QP certification or by a third party on its behalf in accordance with Annex 16 of the EU GMP Guide, to ensure that the imported products are manufactured in accordance with EU GMP rules or equivalent requirements and the MA or clinical trial authorisation.
- 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 responsible for QP certification. Any discrepancy should be investigated under the responsibility of the certifying QP.

## **6. Operations**

- 6.1. The site responsible for QP certification should ensure that an ongoing stability program is in place, as required in Chapter 6 of the EU GMP Guide. 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 site 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 of the EU GMP Guide and applicable detailed guidelines for GMP for IMPs.

## **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 or sponsor for handling complaints, quality defects and product recalls as required in Chapter 8 of the EU GMP Guide. These should be defined in contractual arrangements.