PNR Pharma

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Annex 21

Import and Export

Annex 21

EudraLex

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].

Annex 21

- Came into force on the 21st August 2022
- Scope human, investigational and veterinary medicinal products from outside the EU/EEA.
- Products that enter the EU/EEA with the intention of export only undergo no processing and are not released for placing on the EU/EEA market, are not covered by this Annex.
- Fiscal transactions are not part of this annex.

Annex 21

- 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.
- 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.

Annex 21 - PQS

- 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.
- 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.
- 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

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Annex 21 - Documentation

- 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.
- 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.
- The documentation on the site of physical importation should include, at a minimum, the details of transportation and receipt of the product.

Annex 21 – Documentation Cont'd

- Ordering and delivery documentation should be available for inspection at the site responsible for QP certification or confirmation.
  - 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.
- The QP certification site should ensure that the third country manufacturing site has a record retention policy equivalent to EU requirements.
- The batch certificates and batch documentation must be in a format understood by the importer.

Annex 21 – Documentation Cont'd

If batches have been sub-divided documentation confirming reconciliation of the quantities must be available at the site performing QP certification.

A QP declaration is required to cover all activities performed outside the EU/EEA/UK for UK trials.

For studies in the EU that include activities in the UK the QP declaration must cover the UK activities.

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UK studies that require Full Certification

- Certification requires to be in accordance with Annex 16
- Legal Requirements to comply with Regulation 3 (2) of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) provides further information on the responsibilities of the sponsor(s) as amended by Brexit regulation (2019).

Example – Steps required for IMP imported from India

- Audit of facility
- QP declaration
- PSF Compilation
- Review of Documentation
- Full QP Certification

UK position on Import from EU/EEA

- Importation of clinical trial material from the EU/EEA can be performed using the QP oversight process.
- May be one of two routes:
  - direct to the Great Britain clinical trial site
  - via a Great Britain storage and distribution ‘hub’.

QP oversight

- IMPs are not made available for use in Great Britain clinical trial sites until appropriate
- QP certification in a listed country has been verified by the QP named on the UK MIA(IMP)
- IMPs are only shipped to appropriate Great Britain trial sites detailed within the UK trial application
- Up to date information and documentation relating to the clinical trial and associated PSF are made available by the sponsor to the QP named on the UK MIA (IMP)
- The clinical trial is authorized by the MHRA before IMP is made available to the investigator

Documents for QP oversight

- details of the manufacturing and distribution supply chain.
- the UK Clinical Trial Application form, plus amendments. This should be used to confirm the site responsible for final certification of the finished IMP.
- evidence that the certifying site in the listed country is appropriately licensed and holds a current GMP certificate for the IMP dosage form(s) and associated activities (e.g. manufacture, packaging, testing and / or import from a third country).
- details of the approved Great Britain trial sites from the ethics application, plus any updates or amendments.
- details of each shipment of IMP to Great Britain including the addressees' information. This should be verified against the ethics approvals.
- details of any excursions from the stated storage conditions during shipment, along with any decisions taken by the Sponsor and certifying QP, and the rationale for those decisions.
- details of the responsibilities described in the written agreement between the Sponsor and the listed country MIA(IMP) holder.

Evidence of QP certification

- Batch Certificate
- Statement of Certification
- Access to certifying MIA (IMP) internal system e.g. ERP
- There is no requirement for a UK batch certificate

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Example – Steps required for IMP imported from Poland using QP oversight

- Compilation of quality oversight documentation
- Review of documentation
- Confirmation that clinical site is listed and has appropriate quarantine procedures
- Confirmation of EU QP certification
- Authorisation to clinic to release to IMP

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NIMPs/Auxiliary Medicines and Comparators

- NIMPs
- Unmodified comparators to be labelled in Great Britain prior to QP certification
- Importation from a listed country should be via a WDA (H) using a RPi
- Importation from a country not on the list requires a manufacturers licence.

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Northern Ireland Protocol

Northern Ireland

- IMPs
- QP certification done in GB will enable supply of IMP to Northern Ireland.
- QP certification in the EU/EEA will also enable supply of IMP to Northern Ireland via Great Britain.
- Batch testing may be performed outside the EEA including in GB or NI

Import/Export Main Points

- Supply chains are becoming more complex
- Ensure that you receive the required documentation from custom clearance
- Know your supply chain
- Ensure that there is a method that any changes to the supply chain become known to the QP

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Thank You

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Qualified Person (QP) service offering consultancy and EU Pharmaceutical batch certification for clinical trials and marketed products.