KLH-12 version 4

Requirements for Documentation Relating to Compliance with Good Manufacturing Practice in the Submission of Applications for Clinical Trial Authorisation

This guideline supersedes the KLH-12 guideline version 3 effective from September 11, 2024.

This guideline describes the requirements for documentation relating to compliance with Good Manufacturing Practice (GMP) submitted with an application for clinical trial authorisation. It specifies the required documents depending on the status of the investigational medicinal product (authorised vs. unauthorised) and the manufacturing site location (EU/EEA vs. third countries).

This guideline serves as a recommendation.

In accordance with the provisions of Article 61 of Regulation (EU) No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC (Regulation), the manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

Definitions:

Investigational medicinal product – A medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial.

Authorised investigational medicinal product – A medicinal product authorised in accordance with Regulation (EC) No. 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product.

Third countries – The term "third countries" refers to all countries outside the EU and EEA, including countries with an effective MRA and countries in the ICH region.

Manufacturing operations for which compliance with good manufacturing practice (GMP) should be demonstrated – Relevant GMP documents shall be submitted for each **manufacturing site** of the investigational medicinal product and each **batch certification site** of the manufactured and/or imported investigational medicinal product in the EU/EEA. The submitted GMP document should not be older than three years. The site **of physical importation** of investigational medicinal products from third countries into the EU/EEA shall be subject to GMP requirements; however, the submission of these documents is not requested.

A manufacturing site is any site where **manufacturing operations** are carried out. These include total and partial manufacture, as well as the various processes of dividing up, packaging (primary and secondary packaging), labelling (including blinding), and also quality control testing.

Exceptions under which GMP documents are not required are listed in Article 61, paragraph 5 of the Regulation.

Explanation of terms and abbreviations:

IMP – investigational medicinal product

CT – clinical trial of medicinal products for human use

CT applications submitted nationally – clinical trials submitted nationally before 31.1.2023, clinical trials are approved or authorised

CT applications submitted via CTIS – clinical trials submitted via CTIS (EU portal) since 1.2.2023, clinical trials are approved

GMP – Good Manufacturing Practice

EEA – European Economic Area

ICH – International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

MRA – Mutual Recognition Agreement between the Union and third countries

MIA - Manufacturing and Importation Authorisation

Modification of the medical product – manufacturing step associated with any manipulation with the primary packaging of the authorised product. The following operations are not considered to be modifications:

For CT applications submitted nationally – point 42 of Annex 13 of the EU GMP Guide

For CT applications submitted via CTIS – Article 61, paragraph 5 of Chapter IX of the Regulation

Quality control = batch testing; contract laboratories are subjected to the same GMP requirements as all other sites

1. Types of documents to be submitted

1.1. Manufacturing/import authorisation for investigational medicinal products

A GMP document issued by the competent EU/EEA national regulatory authority. This GMP document should list address(es) of the manufacturing and/or import site(s) of the investigational medicinal products and approved manufacturing operation(s) of investigational medicinal products.

If the submitted GMP document is older than three years from issue date and a newer version is not available, a GMP certificate with the date of conducted inspection, which is not older than three years, should also be submitted (see point 1.2).

In the case that **a valid version of manufacturing/import authorisation** for the manufacturer/importer/control laboratory of investigational medicinal products is available **in the EudraGMDP database**, it is not necessary to submit these documents, but a reference to the relevant document (with manufacturing authorisation number (MIA)) in this database is sufficient.

- EudraGMDP database: http://eudragmp.ema.europa.eu/inspections/logonGeneralPublic.do

1.2. GMP certificate for the manufacturer/importer/control laboratory of investigational medicinal products

A GMP document issued by the competent EU/EEA national regulatory authority based on an inspection of the above-mentioned entities. The date of the conducted inspection should not be older than three years (unless otherwise stated in the document), and the certificate should list address(es) of the inspected site(s) of manufacture/import and/or quality control of the investigational medicinal products and the scope of manufacturing operations inspected for investigational medicinal products.

In the case that **a valid version of the GMP certificate** for the manufacturer/importer/control laboratory of investigational medicinal products is available **in the EudraGMDP database,** it is not necessary to submit these documents, but a reference to the relevant document (with the GMP certificate number) in this database is sufficient.

- EudraGMDP database: http://eudragmp.ema.europa.eu/inspections/logonGeneralPublic.do

1.3. Qualified Person's Declaration of the manufacturer/importer of investigational medicinal products

The declaration is issued by a qualified person of the manufacturing/import site (located in the EU/EEA) responsible for batch certification for all drug product manufacturing sites located in third countries. A qualified person certifies that the manufacturing complies with GMP at least equivalent to the GMP in the EU.

The declaration should not be older than three years, unless otherwise stated. The document is issued for a specific clinical trial and contains following information: EudraCT number (for *CT applications submitted nationally*) or EU CT number (for *CT applications submitted via CTIS*) of the trial, drug product name(s), range of manufacturing operations for each concerned manufacturing site.

- Template for QP declaration: „*Template for the qualified person's declaration equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries*" EudraLex - Volume 10 (europa.eu) (chapter III Quality) / 2013-12_qp_template_imp.pdf (europa.eu)

If there are specific arrangements provided for mutual recognition agreements (MRA) between the EU and third countries in the scope of GMP for investigational medicinal products, the qualified person declaration of the manufacturer/importer for this manufacturing site may be replaced with a valid manufacturing/import authorisation or GMP certificate issued by a competent national regulatory authority (see points 1.1 – 1.2).

- MRA up-to-date information: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra

2. Manufacturing operations and corresponding GMP documents required

2.1. Documents required for an unauthorised medicinal product

2.1.1. All manufacturing operations are conducted within the EU/EEA

Required documents:

- A copy of a valid manufacturing authorisation (and, where applicable, its English, Czech, or Slovak certified translation) for the manufacture of investigational medicinal products issued by the competent national regulatory authority and/or a GMP certificate is submitted for each manufacturing site (see point 1.1 or 1.2).

2.1.2. Some of the manufacturing operations are contracted outside the EU/EEA, other manufacturing operations are conducted within the EU/EEA

For use in a clinical trial, all products partially manufactured outside the EU/EEA should be certified by a qualified person of the manufacturer/importer responsible for the batch certification of the investigational medicinal product in the EU/EEA.

Required documents:

- For each site of manufacture and quality control within the EU/EEA, a copy of a valid manufacturing authorisation (and, where applicable, its English, Czech, or Slovak certified translation) for the manufacture of investigational medicinal products issued by a competent national regulatory authority and/or a GMP certificate is submitted (see point 1.1 or 1.2);
- For all sites of manufacture and quality control outside the EU/EEA, the declaration of compliance with the current GMP requirements issued by a qualified person of the manufacturer/importer site responsible for certification of investigational medicinal product is submitted (see point 1.3);
- For the batch certification site of the investigational medicinal product, a copy of a valid manufacturing authorisation and/or GMP certificate for investigational medicinal products is submitted, as follows:
  a) in the scope of the manufacture of investigational medicinal products (in the case that the last manufacturing operation before batch certification of the IMP, i.e., secondary packaging or labelling, is carried out by a manufacturer located in the EU/EEA, and/or
  b) in the scope of the import of investigational medicinal products from third countries (in the case that the last manufacturing operation before batch certification of the IMP, i.e. secondary packaging, or labelling, is carried out by a manufacturer located outside the EU/EEA.

2.1.3. All manufacturing operations (except for batch certification) are carried out outside the EU/EEA.

For use in a clinical trial, all medicinal products manufactured outside the EU/EEA must be certified by a qualified person of the importer.

Required documents:

- For all site(s) of manufacture and quality control outside the EU/EEA, a QP declaration (of compliance with the current GMP) issued by a qualified person of the site responsible for certification of investigational medicinal product is submitted (see point 1.3)
- For the batch certification site of the investigational medicinal product in the EU/EEA, a copy of valid manufacturing authorisation and/or GMP certificate in the scope of import of investigational medicinal products from third countries is submitted (see points 1.1 – 1.2).

2.2. Documents required for an authorised medicinal product (tested or comparator) that is not further modified for the purposes of the clinical trial

2.2.1. The medicinal product has been granted a marketing authorisation in the Czech Republic or in another EU/EEA Member State

CT applications submitted nationally (before 31.1.2023)

- It is the Sponsor´s responsibility to ensure that the product is labelled for clinical trial purposes in

compliance with the requirements of the EU GMP Annex 13 (in the Czech Republic: SÚKL guideline VYR-32 Amendment 13) by a site with valid manufacturing authorisation. If the labelling is carried out in a pharmacy, a manufacturing authorisation is not required (The conditions for clinical trials of medicinal products in pharmacies are further regulated by SÚKL guideline LEK-12).

CT applications submitted via CTIS (after 1.2.2023)

- Authorised investigational medicinal products and authorised auxiliary medicinal products should be labelled in compliance with the requirements of Article 67, paragraph 1 of the Regulation.
- In the cases stated in Article 67, paragraph 2 of the Regulation, Sponsor is responsible for additional labelling of the outer and the immediate packaging of the authorised investigational medicinal product for the purposes of the clinical trial in compliance with section C of Annex VI of the Regulation. The labelling is carried out by a site with a valid manufacturing authorisation. If the additional labelling is carried out in a pharmacy, or in hospitals, health centres or clinics by pharmacists or other persons authorised to carry out such operations, a manufacturing authorisation is not required.

Required documents:

CT applications submitted nationally (before 31.1.2023)

- name and address of the manufacturer carrying out labelling of the investigational medicinal product for the purposes of the clinical trial;
- name and address of the site responsible for certification of the investigational medicinal product relabelled for the purposes of the clinical trial;
- GMP documents for sites carrying out labelling and certification of the investigational medicinal product (see points 1.1 - 1.3 and 2.1.1 - 2.1.3).

CT applications submitted via CTIS (after 1.2.2023)

If the authorised medicinal product in the clinical trial is relabelled according to Article 67, paragraph 2 of the Regulation, the same documents are required as for the clinical trials submitted nationally (before 31.1.2023).

2.2.2. The medicinal product is not authorised in the Czech Republic or in another EU/EEA Member State, but is authorised in a country of the ICH region

CT applications submitted nationally (before 31.1.2023)

- It is the sponsor's responsibility to ensure that the product is labelled for clinical trial purposes in compliance with the requirements of the EU GMP Annex 13 (in the Czech Republic: SÚKL guideline VYR 32 Amendment 13) by a site with a valid manufacturing authorisation. If the labelling is carried out in a pharmacy, a manufacturing authorisation is not required (The conditions for clinical trials of medicinal products in pharmacies are further regulated by SÚKL guideline LEK-12)

CT applications submitted via CTIS (after 1.2.2023)

- The sponsor of the clinical trial is responsible for additional labelling of the outer and the immediate packaging of the authorised medicinal product for the purposes of the clinical trial in compliance with Section C of Annex VI of the Regulation by a site with a valid manufacturing authorisation. If the additional labelling is carried out in a pharmacy, or in hospitals, health centres or clinics by pharmacists or other persons to carry out such processes, a manufacturing authorisation is not required.

Required documents:

- name and address of the manufacturer carrying out labelling of the investigational medicinal product for the purposes of the clinical trial;
- name and address of the site responsible for certification of the investigational medicinal product relabelled for the purposes of the clinical trial;
- GMP documents for sites carrying out labelling and certification of the investigational medicinal product (see 1.1 - 1.3 and 2.1.1 - 2.1.3).

2.2.3. The medicinal product is not authorised in the Czech Republic, EU/EEA, or a country of the ICH region

A medicinal product authorised in another country than those specified in points 2.2.1 or 2.2.2 is considered unauthorised from the GMP point of view. It is necessary to provide full pharmaceutical documentation and relevant GMP documents according to the supply chain (see points 1.1 - 1.3 and 2.1.1 - 2.1.3)

2.3. Required documents for an authorised medicinal product (investigational or comparator) that is further modified for the purposes of clinical trial

In some cases, the sponsor may modify the authorised product, e.g., for the purpose of blinding. A manufacturer who carries out such a modification of an authorised product must comply with the GMP requirements.

Required documents:

- name and address of the site carrying out modification of the authorised medicinal product;
- name and address of the site carrying out labelling and certification of the authorised medicinal product modified for the purposes of the clinical trial;
- GMP documents for sites carrying out modification of the authorised medicinal product, the labelling and certification of the modified authorised medicinal product (see points 1.1 - 1.3 and 2.1.1 - 2.1.3).

Effective legislation/European guidelines:

- Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts, (Act on Pharmaceuticals), as amended
- Decree No. 229/2008 Coll., on Manufacture and Distribution of Medicinal Products, as amended
- *CT applications submitted nationally (before 31.1.2023)*
  - Decree No. 226/2008 Coll., on Good Clinical Practice and More Detailed Conditions for Clinical trials on Pharmaceuticals, as amended
  - Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- *CT applications submitted via CTIS (after 1.2.2023)*
  - Regulation (EU) No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
  - Commission Delegated Regulation (EU) 2017/1569 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections
  - Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014