KLH-12 version 2 Requirements for Certificates of Good Manufacturing Practice in the Submission of Applications for Clinical Trial Authorisation/Notification

This guideline supersedes guideline KLH-12, version 1 as of November 1 2008.

Pursuant to the requirement stipulated in the provisions of Section 57, paragraph 1 and Section 62 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended, manufacture of investigational medicinal products and their import from third countries shall be subject to manufacturing authorisation.
Certificates of compliance with rules of Good Manufacturing Practice (GMP) shall be submitted as part of the dossier for an application for authorisation/notification of a clinical trial.
The requirements for GMP documents to be submitted together with an application for authorisation and notification are the same.

Definitions for the purposes of this guideline:

Investigational medicinal product (hereinafter abbreviated as IMP)
A medicinal product in the stage of development, which takes the form of a test product, comparator or placebo, the manufacture of which is subject to manufacturing authorisation.
Comparator (comparator medicinal product)
A medicinal product against the properties of which the tested medicinal product is compared in the clinical trial.
Manufacturing site
Any site where manufacturing operations are carried out: manufacture of the dosage form, primary and secondary packaging, labelling, quality control, batch release/batch certification of the investigational medicinal product intended for distribution in the EU/EEA, import of investigational medicinal products from third countries to the EU/EEA.
Third countries
So called “third countries” shall be considered all countries outside the EU/EEA, including countries with an effective MRA.

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 not be older than three years and should show the address(es) of the manufacturing or import site(s) of the investigational medicinal products and an approved scope of manufacturing operation(s) in the sphere of investigational medicinal products.

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 on the basis of a performed inspection of the above-mentioned entities. The specified date of inspection should not be older than three years and the certificate should show the address(es) of the inspected site(s) of manufacture/import and/or quality control of the investigational medicinal products and the inspected scope of manufacturing operation in the sphere of investigational medicinal products. In some cases an valid Manufacturing authorisation can be an integral part of a GMP certificate or an Annex to this certificate.

1.3 **Qualified Person Declaration** of the manufacturer/importer of investigational medicinal products
Refer to Annex 1 of this document. The declaration is issued upon the import of medicinal products from a third country to the EU/EEA and certifies that the concerned manufacturing site(s) in the third country comply with current GMP conditions in the EU/EEA.

2. Manufacturing operations and provided documents

2.1 All of the manufacturing operations, i.e. the manufacture of the dosage form, primary packaging, secondary packaging, labelling, quality control, batch release of the investigational medicinal product are conducted within the territory of the EU/EEA:

Required documents:

- A copy of an valid manufacturing authorisation (and, where applicable, its English, Czech or Slovak authenticated translation) for the manufacture of investigational medicinal products issued by the competent national regulatory authority or a GMP certificate for each manufacturing site – refers to article 1.1 or 1.2 .

2.2 Some of the manufacturing operations (the manufacture of the dosage form, primary packaging, secondary packaging, labelling, quality control) are contracted outside the territory of the EU/EEA, other manufacturing operations are conducted within the territory of the EU/EEA:

For use in a clinical trial, all products whose manufacture has been partially conducted outside the territory of the EU/EEA, have to be released by the qualified person of the manufacturer responsible for batch release of the investigational medicinal product in the EU/EEA.

Required documents:

- For the site(s) of manufacture and quality control within the territory of the EU/EEA a copy of an valid authorisation (and, where applicable, together with its English, Czech or Slovak authenticated translation) for the manufacture of investigational medicinal products issued by the competent national regulatory authority or a GMP certificate for each manufacturing site - refers to article 1.1 or 1.2
- For all site(s) of manufacture and quality control outside the territory of the EU/EEA the declaration of compliance with current GMP issued by the qualified person of the manufacturer/importer shall be submitted – refer to Annex 1 .
- For the sites of batch release of the investigational medicinal product by the qualified person, a copy of an valid manufacturing authorisation for investigational medicinal products as follows:
    a) Within the scope of manufacture of investigational medicinal products, if the site concerned also participates in manufacturing operations (e.g. packaging or quality control);
    b) Within the scope of import of investigational products from third countries, if the site does not participate in manufacturing operations, but only in the release of these products.

2.3 All manufacturing operations (except for batch release) are carried out outside the territory of the EU/EEA.

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

Required documents:

- Manufacturing authorisation within the scope of import of investigational medicinal products from third countries for the importer to the EU/EEA.
- Declaration of compliance with GMP conditions issued by the qualified person of the importer for all sites of manufacture and control (refer to Annex 1).

Documents required for the comparator which is not further modified for the purposes of the clinical trial

A. The comparator has marketing authorisation in the Czech Republic or in another EU/EEA Member State

Required documents:

- A copy of valid Summary of the Product Characteristics (SPC) authorised by the regulatory authority of the state from whose market the comparator shall be obtained for the purposes of the clinical trial. The SPC shall be submitted in the language of the source country together with its translation into the English, Czech or Slovak language.

B. The comparator has not marketing authorisation in the Czech Republic or in any other EU/EEA Member State, but it has marketing authorisation in a MRA country or in an ICH Member State (Decree No. 229/2008 Coll., on the manufacture and distribution of pharmaceuticals, Section 11, paragraph 5 (d)).

The sponsor of the clinical trial shall be obliged to ensure that:

- The product is treated for the purposes of the clinical trial (repackaging, labelling) in compliance with Annex 13 to EU GMP (in the Czech Republic: Amendment 13 to SÚKL guideline VYR 32, revision 2) by the entity who is the holder of the manufacturing authorisation;

- For the purposes of use in the clinical trial, the product manufactured outside the EU/EEA is released by the qualified person of the importer.

Required documents:

- Manufacturing authorisation within the scope of import of investigational medicinal products from third countries for the importer to the EU/EEA.
- Name and address of the manufacturer who carries out packaging and labelling of the investigational medicinal product in compliance with effective Czech legislation and in compliance with the clinical trial plan.
- Manufacturing authorisation for the manufacturer who carries out the packaging and labelling of the investigational medicinal product in the relevant scope.
- A document evidencing that the concerned product has received the marketing authorisation in the specified "third country" (an effective SPC approved by the regulatory authority of the MRA country or ICH Member State in the language of the source country with its translation into the English, Czech or Slovak language).

C. The comparator has not marketing authorisation in the Czech Republic, EU/EEA or ICH Member States or a MRA country

A comparator authorised in a country other than specified under (A) or (B) shall be, in terms of GMP, considered non-authorised. For this reason the same requirements shall be applicable as to the investigational medicinal product, i.e. documents as per its manufacturing sites shall be required.

Documents required for a comparator which is further modified for the purposes of the clinical trial

The sponsor may, in some cases, modify an authorised comparator in order to blind the clinical trial. The manufacturer, who conducts such operation of an authorised product, must comply with the GMP conditions.

Required documents:

- For an authorised comparator before modification, a document evidencing that the concerned product has been effectively authorised in the concerned country (an valid SPC approved by the regulatory authority of the Czech Republic, an EU/EEA Member State, a MRA country or ICH Member State in the language of the source country with its translation into the English, Czech or Slovak language);
- Furthermore, GMP documents for the manufacturing site(s) carrying out the modification operation(s) shall be provided as specified in articles 2.1 – 2.3 above.

Effective legislation/European guidance

Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts, (Act on Pharmaceuticals), as amended (Section 57, paragraph 1 and Section 66, paragraph 4)
Decree No. 229/2008 Coll., on the manufacture and distribution of pharmaceuticals
Decree No. 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products
Commission guideline "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial - ENTR/F2/BL D(2003)" (item 4.1.6.)

Explanation of terms and abbreviations:

IMP – investigational medicinal product
CT – clinical trial
GMP – Good Manufacturing Practice
EU/EEA – European Union/European Economic Area
ICH – International Conference on Harmonisation. The Members of the conference are, besides the EU, also the U.S.A. and Japan.
MRA – Mutual Recognition Agreement. The Agreement has been concluded by the EU and Australia, New Zealand, Canada and Switzerland.
Batch release of a medicinal product by the qualified person of the manufacturer = also certification (= release)
Treatment of a batch of the medicinal product = also modification; a manufacturing procedure associated with any handling of the primary packaging of an authorised product. Item 42 of Annex 13 to EU GMP Guide shall not be applicable to treatment.

Qualified Person Declaration of an importer of investigational medicinal products from third countries

EudraCT number: ……..

Number of the manufacturing authorisation within the scope of import of investigational medicinal products from third countries and name and registered office of the holder:
……..

Investigational medicinal product:
……

Sites of manufacture and control of the investigational product outside the EU/EEA (name, full address), specifying the activities carried out:
1)…..
2)…..
3)…..etc.

I hereby declare that I am the qualified person referred to in the above-mentioned authorisation of manufacture/import and that the investigational medicinal product imported to the EU/EEA and used in the clinical trial is/will be manufactured at the manufacturing sites mentioned in items 1) to…x) in compliance with GMP standards equivalent to those of EU/EEA GMP.

I hereby present this declaration on the basis of the following documents: …….

(E.g. a report of audit conducted at the above-mentioned manufacturing sites by the qualified person of the importer or by any of the EU/EEA regulatory authorities, etc.)

Name: ……
Signature: ……
Date: ……..