KLH-19 version 2

Requirements on authorisation/notification of clinical trials on medicinal products – data required for on the pharmaceutical part of the documentation.

This Guideline supersedes Guideline KLH 19 version 1 as of January 21, 2019.

The guideline is issued on the basis and in accordance with the provisions of Section 55 (7) of Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), as amended, and Annex No. 5 to Decree No. 226/2008 Coll., on the Good Clinical Practice and More Detailed Conditions for Clinical trials on Pharmaceuticals as amended.
The Guideline is for recommendation.

Requirements for Pharmaceutical Data

Investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form

Accordingly, no difference is made between tested products and comparators in the submission of pharmaceutical data and data on the placebo are also submitted, if used in the study.

In those cases where a medicinal product not authorised in the Czech Republic is to be used in a clinical trial as a standard medication, relief or rescue medication, it is necessary to submit pharmaceutical data in the same extent as those for investigational medicinal products.

At present, clinical trials are conducted in compliance with Directive 2001/20/EC. Following the coming into force of Regulation (EU) no. 536/2014 of the European Parliament and of the Council, it will be possible, over a transitory period, to conduct clinical trials, either in compliance with Directive 2001/20/EC, or in compliance with Regulation (EU) no. 536/2014 of the European Parliament and of the Council. Following the expiry of the transitory period, it will be possible to conduct clinical trials solely in compliance with the requirements stipulated by Regulation (EU) no. 536/2014. For more details, it is recommended to follow the website of the European Commission and of the State Institute for Drug Control (SÚKL).

The pharmaceutical dossier which is to be submitted within the application for a clinical trial, should be prepared in the CTD format. For information on the structure of the documentation and on the content of individual sections see https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf.

The pharmaceutical part of the dossier corresponds to Module 3. This template is common for all types of medicinal products. It is therefore necessary to adapt the content of the documentation to the particular type of the product. Nevertheless, this template should be followed during assembling of the documentation and if any part of the dossier is omitted, such omission has to be justified.

1. Medicinal Products Obtained through Chemical Synthesis

The required extent of information is defined by the guidance of the European Medicines Agency (EMA) "Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials" CHMP/QWP/185401/2004 or CHMP/QWP/545525/2017, in accordance with the validity of documents published on EMA´s website („home/human regulatory/research and development/scientific guidelines/quality guidelines/specific types of products").

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000796.jsp&mid=WC0b01ac0580028eb3).

2. Medicinal Products of Biological/Biotechnological Origin

The required extent of information is defined by the guidance of the European Medicines Agency (EMA) "Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials" CHMP/BWP/534898/2004 and "Requirements for quality documentation concerning biological investigational medicinal products in clinical trials" CHMP/BWP/534898/2008, in accordance with the validity of documents published on the EMA´s website („home/human regulatory/research and development/scientific guidelines/quality guidelines/biologicals/finished product/investigational medicinal products").
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000951.jsp&mid=WC0b01ac058002956c).

In case the product contains a raw material obtained from human blood or its components, the submitted documentation must meet the requirements defined by SÚKL Guideline REG-60 "Requirements for the Marketing Authorisation of Medicinal Products Manufactured Using Materials Derived from Human Blood or Blood Components", published in SÚKL´s Bulletin no. 5/2001 and on SÚKL´s website (http://www.sukl.cz/) under the Home/Medicines/Marketing authorisation of pharmaceuticals/Details of marketing authorisation/Guidelines and Forms section.

3. Advanced Therapy Medicinal Products

The "Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials" guideline of the European Medicines Agency are not directly applicable to Advanced Therapy Medicinal Products (ATMPs). Nevertheless, the development of pharmaceutical documentation for a clinical trial application involving an ATMP may be based upon this guideline.

In comparison with other investigational biological medicinal products, especially the following points should be taken into consideration:

- If the manufacturing process is continuous and it is difficult to define the active substance and the medicinal product and to clearly distinguish them from each other, the structure of the documentation may be adjusted to reflect this situation and the relevant information may be provided in one section only (either for the active substance, or for the finished product).
- Where the starting material for a manufacture are human tissues and cells or human blood and its components, their donation, procurement and testing should follow the Directive 2004/23/EC or Directive 2002/98/EC, where applicable.
- The extent of the submitted documentation needs to be adjusted to reflect the characteristics of the specific product. The amount of data will differ depending on the used starting material, other raw materials and excipients, the level of manipulation during manufacture, the degree of characterisation of the active substance, and reconstitution prior to the application of the product, if applicable, etc. For this reason, it is appropriate to use a risk-based approach. Please refer also to Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs (EMA/CAT/CPWP/686637/2011).
- The documentation should contain information on all manufacturing steps starting with the donation of the tissues and cells or, where applicable, blood and its components. In case of gene therapy medicinal products, starting materials are considered to be viral vectors and/or cell banks used for the production of the vector or plasmid.
- Typically, the manufacturing process includes neither the final sterilisation step nor viral inactivation/elimination steps. Hence it is necessary to focus more on the safety of all materials entering

the manufacturing process, on microbiological purity monitoring at individual levels, and on the assuring of aseptic manufacture.

- Ensuring two-way traceability (donor-recipient, and recipient-donor) for all materials of human original is absolutely essential.
- The safety/genetic stability of gene therapy products should be demonstrated. Viral vectors should be replication-deficient, if possible. It is necessary to minimise the risk of recombination with endogenous viruses. An essential parameter to be monitored in genetically modified cells is transduction efficacy.
- With regard to the specific features of the ATMPs, in justified cases (such as the use of a fully closed production system, continuous manufacture, short shelf-life, etc.) it is possible to modify the control strategy. For more information, please refer to the guideline of the European Commission "Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products" – section 11.
- Where necessary, partial process validation may be also required, unlike in the practice relevant to other investigational medicinal products.
- Prior to the planning of the development of the medicinal product, it is necessary to take into account the degree of complexity of the ATMP as it may cause difficulties in demonstration of product comparability ,when the substantial changes to the manufacturing process or change of the manufacturing site are implemented.

With regard to the diversity of the ATMP group and the specific features of each individual product, it is recommended to ask for the scientific-advice with the regulatory authority as early as the stage of clinical trial planning, particularly before the first administration of the medicinal product to humans and, thereafter, prior to the main clinical trial which should support the subsequent application for marketing authorisation of the medicinal product.

SÚKL recommends to follow relevant guidances on EMA´s website dedicated to ATMPs ("home/human regulatory/research and development/advanced therapy medicines/scientific guidelines").
(https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products)

4. Radiopharmaceutical Products

According to Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended, radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) integrated for medicinal purposes. Furthermore, the Act on Pharmaceuticals defines radionuclide generators, kits, and radionuclide precursors.

The requirements related to the documentation for radiopharmaceutical products are summarised in the guidance of the European Medicines Agency (EMA) "Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials", CHMP/QWP/185401/2004 or CHMP/QWP/545525/2017, in accordance with the current version of documents provided on EMA´s website („home/human regulatory/research and development/scientific guidelines/quality guidelines/specific types of products").
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000796.jsp&mid=WC0b01ac0580028eb3).
The aforementioned products must, moreover, meet the requirements defined by the European Pharmacopoeia (Ph. Eur.).

Where radiopharmaceuticals not authorised according to the Act on Pharmaceuticals are to be used, SÚKL shall request an opinion from the State Office for Nuclear Safety (SÚJB) as referred to under Section 56, paragraph 3 of the Act on Pharmaceuticals. In compliance with Section 13, paragraph 4 of Decree No 226/2008 Coll., on Good Clinical Practice and Detailed Conditions of Clinical Trials on Medicinal Products, SÚKL may request this opinion from the sponsor.

SÚJB contact address for request for opinion:

Státní úřad pro jadernou bezpečnost
odbor usměrňování expozic
Senovážné nám. 9
110 00 Praha 1

5. Other Required Documents

Good manufacturing practice (GMP) documents have to be submitted for all manufacturing, testing, packaging, labelling, release, and import sites. The requirements related to these documents are summarised in the relevant European legislation (e.g. in Regulation (EU) no. 536/2014 of the European Parliament and of the Council) and in the current version of SÚKL´s Guideline KLH-12.

For the purposes of a clinical trial, all investigational medicinal products (including authorised non-modified products) have to be labelled in the Czech language.

The requirements for labelling of investigational medicinal products to be used in clinical trials are in compliance with Directive 2001/20/EC and they are summarised in SÚKL´s guideline VYR-32 Annex 13 version 1 (translation of "The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products").
For clinical trials performed according to Regulation (EU) no. 536/2014 of the European Parliament and of the Council, the labelling requirements are summarised in chapter X and in Annex VI. In case of clinical trials performed according to Regulation (EU) no. 536/2014, the labelling requirements apply not only to the tested medicinal products, the comparator or placebo, but also to auxiliary medicinal products (such as standard medications, etc.).