KLH-19 version 1 Documents Required for Authorisation of a Clinical Trial on Pharmaceuticals – Requirements Governing the Pharmaceutical Part of the Dossier

This guideline supersedes guideline KLH 19 as of October 21 2008.

3. Requirements for pharmaceutical data

Investigational medicinal products shall mean such active substances, their mixtures , medicinal products or placebo which are either investigated or used as comparators in clinical trials; investigational medicinal product may be also drug products with marketing authorization. When submitting pharmaceutical data, no distinction is made between investigated products and comparators, and data about placebo, if it is used in the study, should also be submitted.

Where a medicinal product without marketing authorisation in the Czech Republic is planned for use in a clinical trial as a standard medication, relief or rescue medication, pharmaceutical data of the same scope as for investigational medicinal products should be submitted.

The pharmaceutical part of dossier to be submitted together with the application for clinical trial should be prepared in the CTD format. Information about the structure of the documentation and the contents of individual chapters may be found at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update_200805/ctd_05-2008.pdf

The pharmaceutical part of the dossier corresponds to Module 3. This specimen is common to all types of medicinal products. Therefore the content of the dossier should be adjusted according to the specific type of the medicinal product. Nevertheless, this specimen should be followed when compiling the documentation and omission of any parts should be justified.

3.1 Medicinal products manufactured by chemical synthesis

Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials CHMP/QWP/185401/2004

3.2 Medicinal products of biological/biotechnological origin

3.2.1 Products without marketing authorisation or with marketing authorisation in countries other than those specified under item 3.2.2

Any information about the active substance and about the medicinal product should comply with the requirements stipulated in the relevant guidelines of the European Medicines Agency (EMEA) and with the requirements laid down in the effective version of the European Pharmacopoeia (Ph.Eur).

Information to be submitted about the active substance(s):

- Name and formula, and nucleotide/peptide/amino acid sequence, if applicable;
- Essential chemical, physical and biological properties of the active substance;
- Names and addresses of all manufacturers, incl. testing sites;
- A brief description of manufacturing process;
- Characterisation of critical steps and of in-process controls in manufacturing process;
- An overview of changes in the manufacturing process of the active substance during development, specifying what manufacturing process has been used at which stage of the clinical trial, or, if applicable, an evidence of comparability of an active substance manufactured by various manufacturing processes;
- Information about cell banks and vectors;
- Evidence of identity and structure;
- Information about impurities arising from the manufacturing process and potential degradation impurities;
- Specifications (quality criteria);
- Control analytical methods;
- Stability data (storage conditions, shelf-life, results of stability studies);
- Characteristics of batches used for preclinical studies and of batches intended for use in the clinical study.

Information to be submitted about the medicinal product:

- Name, pharmaceutical form(s), strength(s);
- Composition, incl. the functions of individual excipients and the quality standard;
- Name and address of manufacturers involved in the manufacture of the given product, incl. the organisation which performs secondary packaging, labelling and blinding of samples, specifying its function in the manufacturing chain;

- Certificate of compliance with the conditions of Good Manufacturing Practice (refers to KLH-12);
- A brief description of manufacturing process (general description of individual steps, incl. blinding, if applicable);
- Characterisation of critical steps and of in-process controls in manufacturing process;
- Pharmaceutical development, in particular changes in the composition in different phases of the clinical trial;
- Specifications (quality criteria);
- Control analytical methods;
- Batch analysis results;
- Stability data for the concerned use, i.e. results of stability studies, proposed shelf-life and proposed storage conditions;
- Information specifying how the product is protected from the risk of transmission of TSE (Transmissible Spongiform Encephalopathy) agents, whether the product contains any raw material from the organs and tissues of ruminants or whether such material was used in the manufacture of any starting material; the presented documentation must be in compliance with the requirements set down in the CPMP/CVMP guideline titled EMEA/410/01 (http://www.eudra.org/emea.html); these requirements are also stipulated in Annex 1 to guideline REG-59 "Requirements for the marketing authorisation of products from the organs and tissues of ruminants and evidence of safeguarding medicinal products from the transmission of animal spongiform encephalopathy agents", published in SÚKL Bulletin no. 4/2001, and are available from the website of SÚKL (www.sukl.cz) in the section Pharmaceuticals/Marketing Authorisation/Guidelines and Forms.

The issue of product safety in respect of the risk of TSE agent transmission has been intensively discussed and is a matter of constant development which may result in modifications to the requirements, recommendations and measures in the EU. The requirements laid down by SÚKL will be updated on an ongoing basis to reflect this development.

- Information about viral clearance/inactivation; the submitted dossier should be in compliance with the requirements set forth in guideline EMEA/CHMP/BWP/398498/05 (http://www.eudra.org/emea.html).
- Where the product contains a raw material derived from human blood or its components, the submitted dossier should be in compliance with the requirements stipulated in SÚKL guideline REG-60 "Requirements for the marketing authorisation of medicinal products whose manufacture involves substances derived from human blood or its components", published in SÚKL Bulletin no. 5/2001 and on the website of SÚKL (www.sukl.cz) in the section Pharmaceuticals/Marketing authorisation/Guidelines and forms.

The scope of data which are required for each chapter of dossier will be consistent with the stage of development of the drug product. It may differ depending on whether it concerns a newly developed substance or only a new product containing a well-established substance, or may vary to reflect the scope, objectives and expected duration of the clinical trial. It may be different for individual phases of the clinical trial – in the initial stages of development; emphasis will be placed on the identification and control of the substance, while the submission of final specifications and complete data concerning the drug substance and the drug product is expected in the end of the entire development. In somecases SÚKL may require an amendment to the data or submission of sufficient quantities of a sample, incl. reference substances necessary for analysis.

3.2.2 Products without marketing authorization in the Czech Republic, but with marketing authorization in the EU Member States and EEA Member States (Iceland, Liechtenstein, Norway) and in ICH countries (U.S.A., Japan)

The following data about the medicinal product should be submitted; these are included in the application form for authorisation/notification of the clinical trial, with the exception of details regarding the marketing authorisation holder which should be presented in an annex:

- Name, pharmaceutical form(s), strength(s);
- Qualitative composition (for comparators e.g. the composition specified in the package leaflet);
- Name and address of the marketing authorisation holder in the country from which the product will be sourced for the purposes of the proposed clinical trial;
- Marketing authorisation number of the product;
- The summary of the product characteristics from the country from which the product will be sourced for the purposes of the proposed clinical trial;
- Data about a possible change to the secondary packaging and labelling for the purposes of the proposed clinical trial, incl. list of manufacturer(s) performing the above-mentioned manufacturing steps; and submission of certificates of Good Manufacturing Practice.

3.2.3 Products wizh marketing authorization in the Czech Republic

The following data about the medicinal product should be submitted; these are included in the application form for authorisation/notification of the clinical trial:

- Name, pharmaceutical form(s), strength(s);
- Active substance(s);
- Name and address of the marketing authorisation holder in the Czech Republic;
- Marketing authorisation number of the product;
- Data about a possible change to the secondary packaging and labelling for the purposes of the proposed clinical trial, incl. list of manufacturer(s) performing the above-mentioned manufacturing steps; and submission of certificates of Good Manufacturing Practice.

3.2.4 Placebo

- Composition, incl. the function of individual excipients and quality standard;
- Pharmaceutical form;
- Name and address of the manufacturer;
- Certificate of compliance with the conditions of Good Manufacturing Practice;
- A brief description of manufacturing process, incl. in-process controls;
- Specification (quality criteria);
- Storage conditions (temperature, shelf-life);
- Evidencing the protection from the risk of transmission of TSE/nvCJD agents shall be governed by the same provision as that specified under item 3.2.1.

3.3 Advanced therapy medicinal products

3.3.1 Cell therapy medicinal products and tissue engineering medicinal products

Cell therapy medicinal products are defined in Section IV of Annex 1 to the Marketing Authorisation Decree No. 228/2008 Coll. Tissue engineering drug products are defined by Regulation No. 1394/2007 of the European Parliament and of the Council.

Any information about the active substance and about the medicinal product should comply with the requirements stipulated in the relevant guidelines of the European Medicines Agency (EMEA) and with the requirements laid down in the effective version of the European Pharmacopoeia (Ph.Eur).

Essential requirements and principles governing medicinal products of biological/biotechnological origin should be followed during the preparation of the dossier. Some parts of the dossier as modelled in the CTD format may be irrelevant to products of certain nature, and they shall not be required. Omission of any part of the dossier, however, should be justified.

Requirements governing the documents to be submitted for cell therapy medicinal products and tissue engineering medicinal products are as follows:

- A description and characteristics of the active substance should be provided;
- The characterisation of the source of the starting material and safety of the starting material should be evidenced;
- The description of the manufacturing process should include, besides other, also the grafting of the starting material and the method of application/administration of the finished product to the patient;
- Microbial, viral, and TSE safety of the medicinal product should be evidenced (control of starting material, control of raw materials used in manufacture, guarantee of aseptic conditions of manufacturing process, etc.);
- A description of the medicinal product should be provided and doses of the medicinal product should be defined;
- Quality data concerning auxiliary materials or auxiliary medical devices forming part of the product should be provided. The emphasis is laid down on evidence of safety, consistence and biocompatibility of the used auxiliary material or device.
- Product specification (quality criteria) should be provided. The selected analytical methods and limits should be fully justified and a description of how the product identity, efficacy, purity, and sterility, besides other, are ensured should be presented. In case the results of certain tests would be available only after the product is administered to the patient, it should be necessary to specify the procedure to be applied if the results of these tests fail to meet the established limits.
- A detailed discussion on potential impurities in the medicinal product originating in the starting material (e.g. types of cells other than the required ones, etc.), applied raw materials (e.g. cultivation media, wash solutions, etc.) and so on, should be provided;
- It is necessary to ensure the traceability of information from the donor to the recipient of the medicinal product and vice versa;
- Shelf-life as well as the storage conditions of the medicinal product should be determined on the basis of the results of stability studies.

3.3.2 Gene therapy medicinal products

Definition of gene therapy medicinal products is provided in Part IV of Annex 1 to the Marketing Authorisation Decree No. 228/2008 Coll.

Any information about the active substance and about the medicinal product should comply with the requirements stipulated in the relevant guidelines of the European Medicines Agency (EMEA) and with the requirements laid down in the effective version of the European Pharmacopoeia (Ph.Eur).
With a view to the fact that the nature and manufacturing processes of gene therapy medicinal products are similar to those of medicinal products of biotechnological origin, the same requirement as specified under item 3.2.1should be applied to the provided dossier. Where certain parts of dossier are omitted, a proper rationale should be provided.
Requirements governing the documents to be submitted for gene therapy medicinal products:

- Information about the particular characteristics of the gene therapy medicinal product, incl. its expression in the target cell population, should be provided as well as information regarding the source, construction, characterisation and verification of the coding gene sequence, together with its integrity and stability. A complete sequence of all genes other than the therapeutic one should also be specified as well as the regulatory elements and the vector skeleton;
- Where genes for antibiotic resistance are used, a it should be discussed and justified in details;
- Information about the characteristics of the vector used for the transfer and transport of the gene should be provided; for products which use microorganisms such as bacteriae or viruses to facilitate gene transfer (biological gene transfer) data about the pathogenicity of the parent strain and its tropism for specific types of tissues and cells should be provided as well as information about the interaction depending on the cellular cycle; for products using non-biological media to facilitate gene transfer the physico-chemical properties of components should be specified individually as well as in combination;
- Where human or animal cells are used as the vector for gene transport, information outlined under item 3.3 shall be provided;
- For authorisation of a clinical trial (referred to as “CT”) with a product containing genetically modified organisms (referred to as “GMOs”), it is necessary to obtain a licence referred to in Act No 78/2004 Coll., on the Use of Genetically Modified Organisms and Genetic Products, as amended by Act No 346/2005 Coll. The decision or the licence issued by the Ministry of Environment (referred to as the “MŽP”) should be submitted by applicant together with other documents during the submission of the application for authorisation of clinical trial or subsequently, but no later than three days prior the timeline for the issue of the final opinion by SÚKL. If the licence is not available before the end of the authorisation procedure, it is not possible to authorise the clinical trial.
- Where a genetically modified organism is used, a brief assessment of environmental impact which may be based upon guideline EMEA/CHMP/473191/06 Corr. should be submitted.

Requirements governing clinical trials on radiopharmaceuticals

- Pursuant to Act No 378/2007 Coll., on Pharmaceuticals and amendments to some related acts (the Act on Pharmaceuticals), as amended, radiopharmaceuticals are medicinal products which, if prepared for use, contain one or more radionuclides (radioactive isotopes) integrated for medicinal purposes.
- Where radiopharmaceuticals which are a source of ionising radiation are concerned, SÚKL shall apply for an opinion of the State Office for Nuclear Safety (SÚJB) in compliance with Section 55 (2) of the Act on Pharmaceuticals. Pursuant to 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 the sponsor to safeguard this opinion.
- For the purposes of assessment of clinical trials on radiopharmaceuticals SÚJB requires the below-listed documents:
    - Safeguarding radiation protection during irradiation;
    - Expert competence of persons who perform the concerned activities;
    - Irradiation programme, incl. data about the counts, age, and gender of intentionally irradiated persons and the scope of planned irradiation;
    - Data about irradiation quality assurance and management;
    - Patient Information/Informed Consent Form.

Contact addresses:

- Státní úřad pro jadernou bezpečnost (State Office for Nuclear Safety), odbor usměrňování expozic (Exposure Control Department), Senovážné nám. 9, 110 00 Praha 1.