KLH-20 version 6 APPLICATION FOR CLINICAL TRIAL AUTHORISATION/NOTIFICATION

This guideline supersedes guideline KLH-20 version 5 as of 10 April 2020.

The guideline is being issued on the basis of and in compliance with the provisions of Section 55(2) of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended, and Section 13 of Decree No 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products, as amended; furthermore, Decree No 427/2008 Coll., on determination of the amount of costs to be reimbursed for specialised tasks performed by the State Institute for Drug Control and the Institute for State Control of Veterinary Biologicals and Medicines, and Annex 1, Table 5 to this Decree.

The guideline is binding.

Submission of an application for clinical trial authorisation/notification in the Czech Republic

Types of applications and timelines:

A. An application for clinical trial authorisation shall be submitted for any clinical trial (hereinafter referred to as "CT") that uses investigational medicinal products (i.e. tested medicinal products or comparators defined by the protocol) and, furthermore, non-investigational medicinal products supplied by the sponsor (such as rescue medication prescribed by the protocol) obtained by **biotechnology methods** or containing substances of **human or animal origin** that have not been authorized.

- in the Czech Republic or
- in other EU Member States,
- regardless of whether they have been authorised in a third country.

SÚKL shall provide its opinion on the application within the timeline of 60 days. In case of clinical trial with advanced therapy medicinal products (i.e. medicinal products for gene therapy, somatic cell therapy or products containing genetically modified organisms and tissue engineered medicinal products), the timeline shall be extended by further 30 days, i.e. SÚKL shall provide its opinion within the timeline of 90 days. In justified cases, the timeline for the assessment of an advanced therapy medicinal product may be extended by further 90 days. The timeline for the assessment of an application for authorisation of a CT on xenogeneic cell-based therapy is not limited in time.

B. A clinical trial notification on which SÚKL shall provide its opinion within the timeline of 60 days shall be submitted for any clinical trial that uses investigational medicinal products (i.e. tested medicinal products or comparators defined by the protocol) and, furthermore, non-investigational medicinal products supplied by the sponsor (such as rescue medication defined by the protocol):

1. obtained by biotechnology methods or containing substances of human or animal origin that have been authorised in the Czech Republic or in other EU Member States (through national, decentralised, mutual recognition or centralised procedure) in an off-label use;
2. **any other medicinal products** (particularly those of chemical origin) that:
   - have not been authorised in the Czech Republic,
   - have been authorised in the Czech Republic, but will be used outside the scope of the marketing authorisation,
   - regardless of whether they have been authorised in another EU Member State or in a third country.

C. A clinical trial notification on which SÚKL shall provide its opinion within the timeline of 30 days shall be submitted for any interventional clinical trial that concerns investigational medicinal products (i.e. tested medicinal products or comparators defined by the protocol) and, furthermore, non-investigational medicinal products supplied by the sponsor (such as rescue medication defined by the protocol) that have been authorised in the Czech Republic, either on the basis of a marketing authorisation issued by SÚKL or by the European Commission (within a centralised procedure) and are used in compliance with the marketing authorisation, i.e. in compliance with the approved summary of the product characteristics (the same indications, defined population, dosage).

- Important note: a medicinal product used in the trial must be identical to the medicinal product placed on the market in the Czech Republic; for the purposes of the application, it is not possible to give the marketing authorisation number while importing the product for the purposes of the clinical trial from

another country.

Supporting documentation necessary for clinical trial authorisation/notification

The specified requirements are based upon the provisions of Act 378/2007 Coll., on Pharmaceuticals, as amended, and of Decree No 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products, and Commission Communication – Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1). The supporting documentation may be submitted in the Czech, Slovak or English language, in electronic format (electronic submission) and in paper for selected documents, as outlined in the table below (List of documents to be submitted along with the European Clinical trial application form).

Electronic submission means the submission of the documentation in the CTD electronic format

- sent via Eudralink (to: posta@sukl.cz);
- sent to the data mailbox;
- provided on a CD ROM or DVD.

Documents in paper could be:

- submitted to SÚKL's mailroom;
- sent to the following address: Státní ústav pro kontrolu léčiv, Oddělení klinického hodnocení, Šrobárova 48, 100 41, Praha 10, Czech Republic

SÚKL prefers submission in electronic format only.

List of documents to be submitted along with the European application form

Document	**Requirement concerning paper and electronic documents**
EudraCT validation	electronic format
Cover letter	electronic format with el. signature **or one** signed copy (if submitted by post)
SÚKL questionnaire (Annex 1)	electronic format
Clinical Trial Application Form (authorisation/notification) in written form	electronic format with el. signature **or one** signed copy (if submitted by post) + XML file
Protocol with all effective amendments (KLH-8 refers)	electronic format
Investigator's Brochure – for preclinical and clinical data, please refer to KLH-9	electronic format
Case Report Forms	electronic format
Investigational Medicinal Product (IMP) Dossier (IMPD) – information within the scope specified by the updated KLH-19 guideline (for all IMPs, i.e. the tested medicinal product, comparator, placebo, rescue or relief medication, if strictly defined by the protocol) - for non-authorised medicinal products, complete pharmaceutical documentation should be submitted; - for non-modified products authorised in the EU/EEA, MRA or ICH region, the SmPC (Summary of Product Characteristics) should be submitted in the language of the source country along with its translation into the Czech or English language; - for modified authorised products, the SmPC should be submitted along with a simplified dossier concerning the modification performed.	electronic format (CTD format)
List of competent authorities to whom the application was also submitted and information about their decisions	electronic format

Copy of the opinion of the multicentre ethics committee, if available	electronic format
If the applicant is not the sponsor, a power of attorney authorising the applicant to act on behalf of the sponsor	An original or an authenticated copy; where a power of attorney is submitted for one entire procedure, only a copy thereof shall be submitted
A copy of an authorisation to use or release genetically modified organisms (if applicable and available)	electronic format
Informed Consent Form in the Czech language and its amendments, if applicable	electronic format
Patient Information Sheet in the Czech language	electronic format
Trial subject recruitment organisation	---
Protocol summary in the Czech language – Annex 2 refers	electronic format (in the .docx format)
A list of all ongoing clinical trials with the same tested medicinal product	electronic format
Viral safety studies	electronic format
Study medication labelling	electronic format
Respective authorisations issued for trials or products of special nature (if available), e.g. GMO, radiopharmaceuticals	electronic format
TSE certificate, if applicable	electronic format
Declaration of GMP status of an active substance of biological origin	electronic format
A copy of the valid manufacturing or import authorisation within the scope adequate to the acts performed, including a Czech or English translation of this document, for all manufacturing sites (manufacture, testing, packaging, labelling, import, release) of the investigational medicinal product (tested medicinal product, comparator, placebo, and rescue or relief medication if applicable) located within the territory of the EU/EEA – as per the requirements stipulated in the effective version of SÚKL guideline KLH-12	electronic format
Declaration of the Qualified Person of the site responsible for final release of the IMP for all manufacturing sites of the medicinal product located outside the territory of the EU/EEA stating that the manufacturing site meets GMP principles effective within the territory of the EU/EEA (if applicable) – pursuant to the requirements stipulated by the effective version of SÚKL guideline KLH-12	electronic format
A representative certificate of analysis for the tested product	electronic format
Trial sites where the CT will be conducted in the Czech Republic (incl. the full name and title of the investigator)	electronic format
Contact point information according to Art. 3.4 of the Directive (to be specified in the Patient Information Sheet)	electronic format

Note: the documentation shall be submitted in the PDF format, unless specified otherwise.

Detailed information for applicants

1. The European Clinical trial application form is available on website of the European Medicines Agency (EMA) at **https://eudract.ema.europa.eu.** This website also contains a detailed instruction how to complete the application.
   - The application shall be completed in the English language, only the trial title should be provided

bilingually, i.e. also in the Czech language.

- Trial sites addresses and names of investigators, incl. titles, should be completed **only** in the Czech language (diacritics are essential in names).

2. Each application for clinical trial authorisation/notification must contain the EudraCT number as an identifier. The number may be obtained from https://eudract.ema.europa.eu.

   https://eudract.ema.europa.eu/ → EudraCT number, CTA & Login for posting results → Create → initially, generate the EudraCT number; thereafter, using this number, generate the application (Clinical trial protocol).

   The EudraCT number must be stated on all documents pertaining to the respective clinical trial (e.g. when submitting amendments to the clinical trial, sending CT progress reports, reporting suspected unexpected serious adverse reactions (SUSARs), **in the text of powers of attorney or employee authorisations,** etc.)

3. Pursuant to Section 112 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter referred to as the "Act"), the applicant shall be obliged to make a payment covering the costs of expert activities conducted in association with the assessment of the application for clinical trial authorisation or assessment of a notified clinical trial on pharmaceuticals in advance of the submission of the application.

   The amounts of reimbursement and the procedure to be taken to make the payment are detailed in the current version of SÚKL guideline UST-29. Pursuant to the aforementioned provision of the Act, SÚKL may, under certain circumstances, waive or reduce the reimbursement of costs – for more details, please refer to the current version of SÚKL guideline UST-24.

4. Pursuant to Section 13(1) of Decree No 226/2008 Coll., on Good Clinical Practice and Detailed Conditions Governing Clinical Trials on Pharmaceuticals (hereinafter referred to as the "Decree"), the application for clinical trial authorisation/notification shall be submitted to SÚKL by the sponsor or by person authorised thereby.

   In case the application for clinical trial authorisation/notification is submitted by other person than the sponsor, a power of attorney or employee authorisation for this person shall be submitted by the sponsor along with each application for clinical trial authorisation/notification. The power of attorney/authorisation shall always be signed by the executive officer of the company or a person authorised thereby. Powers of attorney shall be submitted in the **original** or as an **authenticated copy** of the original where so called "presidial" powers of attorney are concerned; the submission of a copy of a power of attorney concerns authorisation for one entire procedure; in case of employee authorisation, only a copy shall be submitted. Suggested specimen power of attorney and employee authorisation are available from here.

5. Pursuant to Section 51(2)(d) of the Act, a sponsor may only a be a person residing or established within the territory of the Czech Republic or any of the EU or EEA Member State (i.e. EU + Iceland, Liechtenstein, Norway), or a person who has appointed an authorised representative meeting this condition.

   In case the application or notification is submitted by the sponsor with its registered office outside the territory of the Czech Republic or the EU, along with the application they shall be obliged to submit a power of attorney for the person (legal or natural) residing or established within the territory of the Czech Republic or the EU/EEA ***(legal representative)***. The address of an organisational unit (branch) of a sponsor from a third country in the Czech Republic or EU/EEA cannot be considered the sponsor's registered office. In such a case, the sponsor shall be obliged to appoint its authorised representative as referred to under Section 51(2)(d) of the Act.

6. The aforementioned requirements shall apply also to clinical trials submitted by representatives of medical professionals or professional societies (grant studies, academic research), nevertheless, to simplify the procedure, the Clinical Trials Unit provides free consultations regarding the completion of the application form and submission of the required documentation.

7. The application may be submitted together with a completed form "Certificate of authorisation/notification of clinical trial for customs procedure" which will be sent to the specified address once the decision on the conduct of the clinical trial is issued.

8. When submitting applications for bioequivalence studies, the Investigator`s Brochure (IB) of the tested medicinal product may be replaced with the Summary of Product Characteristics (SmPC) for the comparator (original) product. Where differences between the IB (or proposed SmPC) for the tested product and the SmPC of the original product exist, they should be provided by summary of changes.

9. The cover letter should contain the following information:

   - A complete lists of documentation, including version numbers and version dates.
   - In case the clinical trial is being submitted within the national phase 3 VHP, this fact should be highlighted and the VHP number should be specified in the cover letter.
   - It is necessary to explicitly state that the documentation is identical to the one approved within the VHP and to provide an e-mail from the VHP coordinators. This shall apply also to submissions of subsequent amendments.
   - In case of resubmission of CT application, the applicant should mention in a cover letter any changes to the previous application submission in the text. Unchanged documentation shall not be repeatedly submitted, but only referred to.

- Where an Integrated Protocol Design is concerned (a protocol including two separate parts of a clinical trial, where different trial subjects are to be enrolled in part one and part two), it shall be mentioned whether both parts of the protocol are to be conducted in the Czech Republic. In case only one part is to be conducted in the Czech Republic, it shall be specified which one and where the other part of the protocol will be/has been conducted.
- In case the CT has been rejected in any member state, this fact should be mentioned in the cover letter.
- Where a “resubmission” is concerned, this should be also mentioned and appropriately highlighted in the CTA.
- In case a medical device supplied by the sponsor is to be used within the scope of the CT for the purposes of the CT, it is necessary to submit the manufacturer's declaration of conformity, CE certificate from the notified body, and instructions for use in the Czech language (glucometers, thermometers, etc.). This shall be applicable to all medical devices not coming from the Czech market. Where a clinical trial on an investigational medicinal product and, concurrently, a clinical investigation of a medical device are concerned, this fact should be highlighted in the cover letter. In such a case, it is necessary to submit an application for clinical trial authorisation/notification, including documentation referred to hereunder to the Clinical Trials on Pharmaceuticals Unit and, at the same time, submit a notification of the intention to perform a medical device investigation to the Medical Device Clinical Investigations and Vigilance Unit. When notifying of the intention to perform clinical investigation of a medical device, please adhere to the instructions specified at: https://www.niszp.cz/cs/klinicke-zkousky/podani-zadosti-o-povoleni-provedeni-klinicke-zkousky
- The cover letter must be signed and the applicant’s signature confirms that the sponsor declares that the provided information is complete, the attached documents contain an exact list of available information, the clinical trial will be conducted in compliance with the protocol, SUSAR reporting and notification of information regarding results will be conducted in compliance with applicable legal regulations.

Other documentation – requirements:

- Where the written information for investigators regarding the use of authorised medicinal products has been replaced with the Summary of Product Characteristics, and the conditions of use within the clinical trial differ from those that have been authorised, an overview of relevant clinical and nonclinical data supporting the use of the investigational medicinal product in the clinical trial shall be submitted along with the Summary of the Product Characteristics.
- Where the investigational medicinal product is identified in the protocol solely by its active substance, the sponsor should select one Summary of Product characteristics as equivalent to the IB for all medicinal products that contain the active substance and are used at any of the trial sites.
- In case of an application for authorisation/notification of a clinical trial on a medicinal product that has already been administered to humans, it is necessary to provide the summaries of all available data from the previous clinical trials and experience in humans with the proposed investigational medicinal products. All of the studies should be conducted in compliance with the principles of Good Clinical Practice (GCP). For this reason, SÚKL requires that the sponsor/applicant submit a declaration of GCP conformity of the listed clinical trials. If any of the listed clinical trials have been conducted in a third country, this fact should be highlighted.
- The submitted documentation should, furthermore, contain a brief and comprehensive summary that would critically analyse nonclinical and clinical data from the perspective of potential risks and benefits of the proposed trial, unless such information is provided in the protocol. If it is contained in the protocol, the applicant should cross-reference the respective part of the protocol. In case any clinical trial was terminated early, this fact should be mentioned together with the reason for the early termination.

Documentation required for medical devices used within the scope of a CT:

- A list of used medical devices to be supplied for the purposes of the CT by the sponsor
- For each medical device: CE certificate + manufacturer's declaration of conformity (EU Declaration of Conformity)
- Please submit also instructions for use in the Czech language

Annexes:

Annex 1 – SÚKL Questionnaire

Annex 2 - Protocol Summary Outline in the Czech Language

Annex 3 - Requirements for the Submission of Pharmaceutical Data for IMPs Previously Assessed by SÚKL

Annex 1

SÚKL Questionnaire

Study title (exact title of the protocol in the original language):

Shortened study title:

Protocol number:

EudraCT number:

	YES	NO
Was the CT rejected by any ethics committee in the Czech Republic or abroad?	☐	☐
If YES, specify the reason:		
Was the CT rejected by any EU or third-country regulatory authority? **NA** ☐	☐	☐
If YES, specify the reason:		
Was Scientific Advice issued for the CT?	☐	☐
If YES, please submit it.		
Is the CT part of a PIP (Paediatrics Investigational Plan)**?**	☐	☐
If YES, specify the PIP number.		
Is the CT being submitted as part of a VHP (Voluntary Harmonisation Procedure**)?**	☐	☐
If YES, provide the VHP number and declaration of conformity of the submitted documentation.		
Is the CT a first-in-human trial?	☐	☐
Does the CT use any products containing addictive or psychotropic substances?	☐	☐
If YES, please specify which ones.		
Does the CT use a radiopharmaceutical product?	☐	☐
If YES, submit the opinion of the State Office for Nuclear Safety (SÚJB).		
Does the CT use a GMO (genetically modified organism**) containing product?**	☐	☐
If YES, provide the opinion on the Czech Ministry of the Environment.		
Was the tested product previously used in a CT in the Czech Republic?	☐	☐
If YES, please provide the trial identification (EudraCT number, SÚKL file no.) + attach the documents referred to under Annex 3.		
Was the non-authorised comparator product previously used in a CT in the Czech Republic?	☐	☐
If YES, please provide the trial identification (EudraCT number, SÚKL file no.) + attach the documents referred to under Annex 3.		

Date:	**Name:**	**Signature:**

Annex 2

Protocol Summary Outline in the Czech Language

(An outline intended as assistance when drafting the summary; this is not a fill-in document; the sponsor may alter the format as necessary; nevertheless the requirements mentioned below should be reflected)

EudraCT number
Study title
Protocol number (date, version)
Phase
Justification of the proposed clinical trial (rationale)
Risk/benefit assessment
Used medicinal products

- IMP (including active substance, MA status and mechanism of action)
- comparator
- placebo
- any prescribed rescue or relief medication

Number of trial subjects

- total
- planned to be enrolled in the Czech Republic

Purpose of the clinical trial – rationale and justification of the proposed study
Study plan (including description of measures adopted to eliminate bias)
Indication selected for the concerned clinical trial
Objectives

- primary objectives
- secondary objectives

Method of evaluation – endpoints

- efficacy endpoints
- safety endpoints
- tolerability endpoints
- others

Selection of population

- inclusion criteria
- exclusion criteria
- withdrawal criteria

Treatment

- treatment duration, doses and dosing schedule, max. daily dose
- concomitant treatment
- description of follow-up treatment after the end of the study, if applicable

Visit and follow-up system
Statistics – a brief description of methods applied for the evaluation of results

Annex 3

Requirements for the Submission of Pharmaceutical Data for IMPs Previously Assessed by SÚKL

If the investigational medicinal product has already been assessed by the State Institute for Drug Control (hereinafter referred to as "SÚKL"), it is necessary to submit a sponsor's declaration specifying whether any changes have or have not been made to the pharmaceutical documentation (IMPD) compared to the previously approved version. The declaration (see Annex 1) has to contain a reference to the previously assessed pharmaceutical documentation (product name, EudraCT number of the clinical trial, SÚKL file no.).

In case no changes have been made, the following shall be submitted:

1. Sponsor's declaration (Form 1 refers);
2. For the active substance(s), finished medicinal product(s), comparator(s), and placebo: a list of all manufacturers, including Good Manufacturing Practice documents, specifications, shelf-life and storage conditions; where a protocol of autonomous shelf-life extension has been approved, this approved plan shall be also submitted (Form 2 refers).

In case changes have been made, the following shall be submitted:

1. Sponsor's declaration (Form 1 refers);
2. A list of all changes in IMPD – either in the form of a list of amended chapters and a summary of the individual changes made, or in a "now/then" table comparing the current and previous version;
3. The entire IMPD, or only those chapters that have been amended (so called "simplified IMPD").
4. For the active substance(s), finished medicinal product(s), comparator(s), and placebo: a list of all manufacturing sites, including Good Manufacturing Practice documents, specifications, shelf-life and storage conditions; where a protocol of autonomous shelf-life extension has been approved, this approved plan shall be also submitted (Form 2 refers).

Form 1

Sponsor's declaration regarding the status of pharmaceutical documentation compared to the previously assessed version

Sponsor of the clinical trial
(company name and address)

This is to declare that since the last clinical trial

(EudraCT number) *(SÚKL file no.)*

on medicinal product

(name, strength, pharmaceutical form)

*no changes to the quality of the product and its manufacturing process have been made.

*the following changes to the quality of the product and its manufacturing process have been made: *(please specify)*

Date	Signature of sponsor's responsible person	Stamp

* Delete as appropriate

Form 2

Requirements governing the submitted summary of pharmaceutical data

Active substance

1. Manufacturer(s)
Specify the complete manufacturing chain (manufacturing as well as testing sites).

2. Specification
Specify the current version of the specification.

3. Shelf-life
Specify the approved shelf-life and storage conditions for the active substance. In case an autonomous extension protocol has been approved, provide the approved plan.

Investigational medicinal product

1. Manufacturer(s)
Specify the complete manufacturing chain (manufacturing as well as testing sites, packaging and labelling sites), including Good Manufacturing Practice (GMP) documents (for requirements, please refer to the current version of guideline KLH-12).

2. Specification
Specify the current version of the specification.

3. Shelf-life
Specify the approved shelf-life and storage conditions for the IMP. In case an autonomous extension protocol has been approved, provide the approved plan.

Comparator / Placebo

1. Manufacturer(s)
Specify the complete manufacturing chain (manufacturing as well as testing sites, packaging and labelling sites), including GMP documents (for requirements, please refer to the current version of guideline KLH-12), if the comparator/placebo has not been authorised.

2. Specification
Specify the current version of the specification, if the comparator/placebo has not been authorised.

3. Shelf-life
Specify the approved shelf-life and storage conditions for the comparator/placebo. In case an autonomous extension protocol has been approved, provide the approved plan.

Date	Signature of sponsor's responsible person	Stamp