KLH-20 version 4 APPLICATION FOR AUTHORISATION/NOTIFICATION OF CLINICAL TRIALS

This guideline supersedes guideline KLH-20, version 3 as of November 1 2008.

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

Types of applications and timelines:

A) An application for clinical trial authorisation shall be submitted for each clinical trial (hereinafter referred to as CT) which uses investigational medicinal products (i.e. tested, comparator or obligatory rescue medications established and ordered by the protocol) obtained by **biotechnology** or containing **substances of human or animal origin** which are not authorised in the Czech Republic or in other EU Member States, regardless of the fact whether they are authorised in any other third country. SÚKL shall provide its opinion on the application within 60 days. Where medicinal products for modern therapies are concerned (i.e. medicinal products of the nature of gene therapy, somatic cell therapy, or containing genetically modified organisms, and as of January 1 2009 also medicinal products for tissue engineering), the timeline shall be immediately extended by further 30 days, i.e. SÚKL shall provide its opinion within the timeline of 90 days. In justifiable cases the period for the assessment of a medicinal product for modern therapies may be extended by further 90 days. The timeline for the assessment of an application for authorisation of a clinical trial involving a xenogenic cell therapy shall not be restricted.

B) Notification of a clinical trial, for which SÚKL shall provide its opinion within 60 days, shall be binding for any clinical trial using investigational medicinal products (i.e. tested, comparator or obligatory rescue medications established and ordered by the protocol):

a) obtained by biotechnology or containing substances of human or animal origin authorised in the Czech Republic or in other EU Member States (by any type of marketing authorisation procedure, incl. centralised procedure), which, however, are not used in accordance with the marketing authorisation.

b) **any other medicinal products** which:
   - are not authorised in the Czech Republic,
   - are or are not authorised in EU Member States,
   - are or are not authorised in a third country,
   - are authorised in the Czech Republic, but are used outside the scope of marketing authorisation.

C) Notification of a clinical trial on which SÚKL shall provide its opinion within 30 days, shall be binding for each intervention clinical trial involving investigational medicinal products (i.e. tested, comparator or obligatory rescue medications established by the protocol) authorised in the Czech Republic either by a decision issued by SÚKL or by the European Commission (in a centralised procedure), and used in accordance with the marketing authorisation, i.e. in compliance with the approved summary of the product characteristics (the same indications, population defined, dosage). Important note: a medicinal product used in the study must be identical to the medicinal product placed on the market in the Czech Republic; it is not acceptable to specify a marketing authorisation number of a medicinal product authorised in the Czech Republic and to import the product intended for use in the clinical trial from another country!

Guidance for applicants:

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

2) The application is available from the EMEA website at *www.emea.europa.eu*. The completed application shall be submitted in hard copy and electronically in the XML format on a CD or DVD.

3) Preferably, the application should be completed in the English language or, if appropriate, in the Czech language (where the Czech language is used, it is advisable to give at least the study title in the English language, because the data are entered into the EMEA database in the form in which SÚKL receives them in the electronic format).

4) Each application for authorisation/notification of a clinical trial has to contain the EudraCT identification number, which may be obtained from *www.emea.europa.eu* – the right column, section EU TELEMATICS – EudraCT website – Access to EudraCT Application – EudraCT number step 1 = to obtain the security code. The same

procedure should be then repeated up to EudraCT step 2 = to obtain the EudraCT number. Where the EudraCT number is allocated via e-mail it is necessary to print out the e-mail and to attach it as a certificate of allocation of the European identification number. The EudraCT number must be thereafter shown on all documents pertaining to the concerned clinical trial (e.g. when amendments to clinical trial, SUSARs, etc. are submitted).

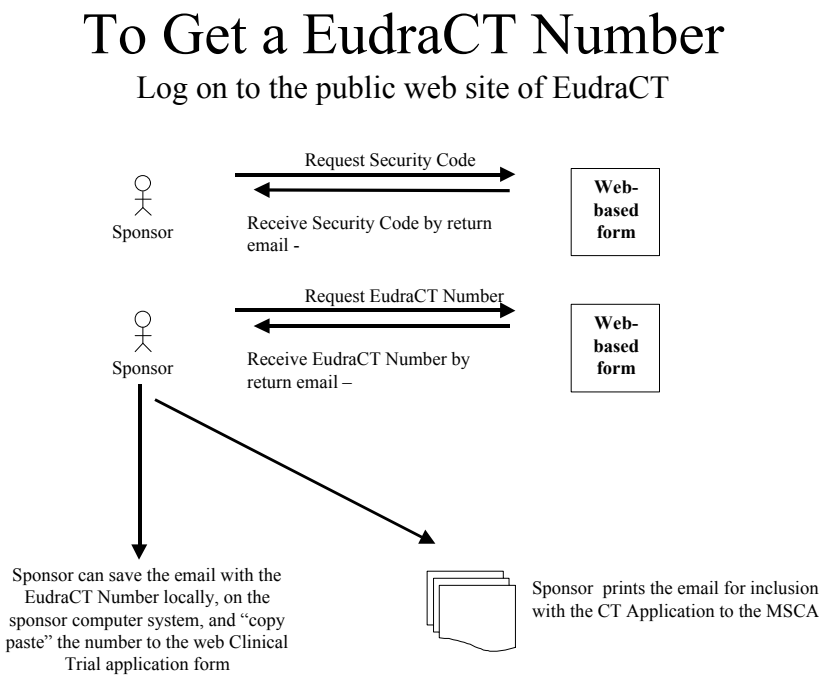
How to obtain a EudraCT number:

Steps 1 and 2, *described below, provide access to electronic forms which must be submitted for you to obtain the EudraCT number*

EudraCT number has the format of YYYY-NNNNNN-CC, where:
YYYY is the year of issue of the number,
NNNNNN is a six-digit sequence number,
CC is a control number.

EudraCT number Step 1 – Request for security code
Step 1 results in obtaining a verified security code. This security code will be sent to the e-mail address you (the applicant) provide in the relevant form. The code is necessary for you to be able to complete the application for allocation of the EudraCT number. It is valid only for a single EudraCT number and expires after 24 hours, if the EudraCT number is not generated.

EudraCT number **Step 2 – Request for EudraCT number**
This is the key part of the application for EudraCT number, which enables you (the applicant) to obtain your EudraCT number. The EudraCT number will be sent to the e-mail address provided by you (the applicant) in the relevant form.



5) Pursuant to Section 112 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), as amended (hereinafter referred to as the Act), in advance of the submission of the application the applicant shall be obliged to reimburse the costs of expert activities conducted in respect of the assessment of the application for clinical trial authorisation or in respect of the assessment of a notified clinical trial on pharmaceuticals. The amounts of costs to be reimbursed and the payment procedure are specified in the latest version of SÚKL guideline UST-29. The above-mentioned provision of the Act, moreover, stipulates that SÚKL may waive the reimbursement of costs under certain conditions – relevant details are provided in the latest version of SÚKL guideline UST-24.

6) Pursuant to Section 13, paragraph 1 of Decree No 226/2008 Coll. on good clinical practice and detailed conditions of clinical trials on medicinal products (hereinafter referred to as the Decree) the application for authorisation/notification of clinical trials shall be submitted to SÚKL by the sponsor or by a person authorised thereby. Where the application for authorisation/notification of a clinical trial is submitted by a person other than the sponsor, the sponsor's authorisation issued for this person shall be submitted together with any application or notification. The authorisation must be submitted in the **original** or in an **authenticated copy** of the original.

Suggested specimen authorisation is provided as independent information on SÚKL's web site, section Clinical trials, Information.

Pursuant to Section 51, paragraph 2 (d) of the Act, the sponsor may be only a person residing or established within the territory of the Czech Republic or any of the EU Member States, or where applicable, a person who has appointed an authorised representative satisfying this condition.

Where the application or notification is submitted by a sponsor residing outside the territory of the Czech Republic or the EU, he/she shall be obliged to submit the power of attorney for the person (natural or legal) whose registered office or address of residence is within the territory of the Czech Republic or the EU (***legal representative)*** together with the application. The registered office of an organisational unit of a sponsor from a third country in the Czech Republic or in the EU cannot be considered the sponsor's registered office; in this case the sponsor must appoint its legal representative as stipulated by Section 51, paragraph 2 (d) of the Act.

Moreover, it is necessary to submit an authorisation for all persons who act on behalf of the sponsor for the clinical trial in question. This obligation shall not apply to contact persons unless they act on behalf of the sponsor or persons authorised thereby (acting on behalf of the sponsor shall mean e.g. the submission of the application, i.e. its signature).

The sponsor may authorise a single person established or residing within the territory of the Czech Republic or the EU to act for several clinical trials thereof, incl. those trials which will be notified in future or those for which authorisation will be sought in future. This authorisation should be limited in time and shall not exceed the period of one year, with regard to possible changes in the relationship between the sponsor and the authorised person. The person submitting the application to SÚKL shall send the original of such authorisation together with the notification or application for authorisation of the first clinical trial and its copies shall be attached to any other application for authorisation/notification of a clinical trial.

7) In the case of clinical trials which are submitted by the representatives of medical professions or by professional societies (grant studies, academic research), the above specified requirements must be also observed; nevertheless, to simplify the procedure, the department of Clinical Trials provides consultations in respect of the completion of applications and submission of required documentation.

Source materials required for authorisation/notification of clinical trials

The requirements described are based on the provisions of the Act on Pharmaceuticals No 378/2007 Coll., and Decree No 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products. Source materials are to be submitted in the Czech, Slovak or English language, in the below given number of copies to SÚKL mail room, or sent to the following address: Státní ústav pro kontrolu léčiv, oddělení klinického hodnocení, Šrobárova 48, 100 41 Praha 10.

Overview of documents to be submitted together with the European Application form to regulatory authorities of Member States and to ethics committees, indicating the documents which must be submitted together with the SÚKL application (part K of the European Application form)

Document	**Required by SÚKL**	**No. of printed copies to be submitted as CT documentation**
EudraCT certificate	Yes	1
Cover letter	Yes	1
Application form for authorisation/notification of a clinical trial in hard copy	Yes	2
Disk with the EudraCT application form in XML format	Yes	1
Protocol and all effective amendments thereto (KLH-8 refers)	Yes	2
Investigator's Brochure – preclinical and clinical data - KLH-9 refers	Yes	2
Case Report Forms (if CRFs are generated electronically, at least one printed report form is required)	Yes	1
Investigational medicinal product dossier (IMPD) – scope of information to correspond to the requirements specified in the updated version of KLH-19 (for all investigational medicinal products, i.e. the tested medicinal product, comparator, placebo, rescue or relief medication, if strictly required by the protocol)	Yes	1

Simplified investigational medicinal product dossier for known products as per the requirements specified in the updated version of KLH-19	Yes	1
Summary of the Product Characteristics (SPC; REG-74 refers) for products authorised in the Czech Republic (via national or centralised procedure in the EU) and used in compliance with the marketing authorisation	Yes	2
List of regulatory authorities to whom the application has been submitted, and decision details	Yes	1
A copy of the opinion of the ethics committee, if available	Yes	1
Where the applicant is not the sponsor, an authorisation issued for the applicant to act on behalf of the sponsor	Yes	1
A copy of the licence to use or release genetically modified organisms (if applicable and available)	Yes	1
Informed Consent Form in the Czech language and its amendments, if applicable	Yes	2
Information for trial subjects in the Czech language	Yes	2
Subject recruitment organisation	No	
Protocol summary in the Czech language –Annex 1 refers	Yes	2
An overview of all active clinical trials with the same tested medicinal product	Yes	1
Peer review for the clinical trial, if available	No	
Ethical assessment carried out by the principal investigator or coordinating investigator	No	
Viral safety study	Yes	1
Specimen labelling in the national language	No	
Relevant authorisations issued for the trial or products of special nature (if available), such as GMO, radiopharmaceuticals	Yes	1
TSE certificate, if applicable	Yes	1
Declaration of GMP status of an active substance of biological origin	Yes	1
A copy of the manufacturing authorisation pursuant to Article 13.1 of the Directive, stipulating the scope of this authorisation, if the investigational medicinal product is manufactured in the EU and has not been authorised in any EU Member State	Yes	1
Declaration of the qualified person of importer from third countries stating that the manufacturing site complies with GMP requirements (if applicable)	Yes	1
A copy of the manufacturing authorisation for importers from third countries as referred to in Article 13.1 of the Directive. For importers from third countries, manufacturing authorisation is required.	Yes	1
A representative certificate of analysis for the tested product.	Yes	1
Planned trial sites (incl. the full name and title of the investigator)	Yes	1
CV of the coordinating investigator in the concerned Member State for multicentric CTs	No	
CV of each investigator responsible for the conduct of the CT in individual sites in the Member State (principal investigator)	No	
Information about auxiliary personnel	No	
Information about the contact person referred to in Art. 3.4 of the Directive (specified in Patient Information)	Yes	2

Insurance coverage or provision of compensations for injuries to health or death due to participation in the CT	No
Liability insurance concluded for the investigator and sponsor	No
Compensation for the investigator	No
Compensation for trial subjects	No
Agreement concluded by the sponsor and trial sites	No
Certificate of agreement concluded by the sponsor and the investigator, unless provided in the protocol	No
Agreement concluded by the investigators and trial sites	No

Note:

1) The cover letter must contain the following details:

- a list of submitted documents, incl. versions and version dates;
- if the clinical trial has been declined by an ethics committee or by another regulatory authority, this fact must be stated, giving the reason for the rejection;
- if the clinical trial uses a product previously assessed by SÚKL for the purposes of another CT, this has to be stated including the identification of the previous CT and a comparative table; it is not necessary to re-submit pharmaceutical documentation, a reference to the previous one and specification of changes thereto shall be considered sufficient;
- where a Scientific Advice has been issued for the study, this fact must be mentioned and results thereof submitted;
- where the study is included in PIP (Paediatrics Investigational Plan), this fact must be mentioned;
- for clinical trials on products containing GMOs the opinion of the Czech Ministry of Environment (MŽP ČR) has to be submitted.

2) SÚKL requests that all documentation is submitted also in electronic format.

Annex 1 – Syllabus for Protocol Summary in the Czech language

Syllabus for Protocol Summary in the Czech language

(The purpose of the syllabus is to assist in compiling the Summary; it is not a document intended for completion; the sponsor may alter the format to suit their needs, but should respect the below mentioned requirements.)

EudraCT number

Study title
Protocol number (date, version)
Phase
Rationale of the proposed clinical trial
Risk/benefit assessment

Applied medicinal products

- investigational (incl. active substance, marketing authorisation status, and mechanism of action);
- comparator;
- placebo;
- rescue or relief medication, if obligatory.

Number of trial subjects

- total;
- planned for inclusion in the Czech Republic.

Purpose of the clinical trial - rationale and justification of the proposed study

Study plan (incl. a description of measures adopted to minimise bias)

Indication chosen for the concerned clinical trial

Objectives

- primary objectives
- secondary objectives

Method of evaluation – monitored parameters of:

- efficacy;
- safety;
- tolerance;
- others.

Selection of population

- inclusion criteria;
- exclusion criteria;
- criteria for withdrawal from the study.

Therapy

- treatment duration, doses and dosing schedule, max. daily dose;
- concomitant therapy;
- organisation of further treatment following study completion, if applicable.

Visit and control system

Statistics – a brief description of methods used for the evaluation of results