GUIDELINES FOR CLINICAL TRIALS OF DRUGS AND MEDICAL DEVICES

**Clinical trials of drugs are divided into 4 phases:**

The first use of a newly discovered drug in humans is undertaken **in phase 1.** In this phase the fate of the drug in the organism (pharmokinetics) is tried and tested, its compatibility is determined, as well as the metabolic and pharmacological effects of the drug reported from testing on animals, and the dosage of the drug is determined. The researchers in this phase are as a rule clinical pharmacologists.

In phase 2 of clinical trials, the possible therapeutic effects of the drug being tested are determined. In that phase the drug is used for the first time on patients. Phase 2, especially its first part, 2b, is conducted in clinical pharmacology departments.

Clinical trial phase 3 precedes the registration of the drug, and is expected to provide answers to questions such as: the primary indications, the dosage and dosing regime, side effects, interaction with other drugs or food.

**All clinical trials conducted for drugs already registered for a specific indication are part of phase 4 clinical trials.**

**When registering your research which is in clinical phases 1, 2 3 or 4, please apply to the Central Ethics Committee, which is with the Agency for Drugs and Medicinal Products (**[**http://www.halmed.hr/O-HALMED-u/Sredisnje-eticko-povjerenstvo-SEP/**](http://www.halmed.hr/O-HALMED-u/Sredisnje-eticko-povjerenstvo-SEP/)**) and study the following provisions of the Act on Drugs and Medical Products:**

2. CLINICAL TRIALS OF MEDICINAL PRODUCTS

Article 10

Clinical trials of a medicinal product shall be conducted only in cases where the Central
Ethics Committee and the ministry responsible for health (hereinafter the Ministry) assess that
the expected benefits for an individual patient or other present or future patients outweigh the
anticipated risks.

Article 11

(1) The clinical trial sponsor referred to in Article 3 item (30) of this Act (hereinafter: the
clinical trial sponsor) or representative of the sponsor referred to in Article 3 item (31) shall
submit the application for conducting a clinical trial.

(2) Clinical trial sponsors that are not established in the European Union shall designate
authorised representatives with a seat in an EU Member State.

(3) A clinical trial sponsor may assign all or a part of their responsibilities to another natural
or legal person, however this shall not relieve them of their responsibility for the relevant
clinical trial.

(4) Applications for non-interventional trials shall be submitted by the marketing
authorisation holders in the Republic of Croatia, or the holders of the authorisations granted
through the centralised procedure or the representatives of the marketing authorisation
holders.

Article 12

(1) The Central Ethics Committee shall give opinions on the procedure for approval of
clinical, non-interventional and non-commercial trials in the Republic of Croatia.

(2) The Ministry shall grant approval for the conduct of clinical trials of medicinal products,
including the non-commercial trials referred to in Article 163 paragraph 1 of this Act.

(3) The Agency shall grant approval for the conduct of non-interventional trials, with the
exception of the non-interventional trials referred to in Article 163 paragraph 1 of this Act.

Article 13

The Minister shall issue an ordinance laying down how the Central
Ethics Committee is to submit its opinions and give approval for clinical, non-interventional and non-commercial trials of medicinal products, as well as the documents required.

Article 14

(1) The Central Ethics Committee shall issue an opinion in writing on the acceptability of the
proposed clinical, non-interventional and non-commercial trial within the period of up to 30
days from the receipt of a correctly filed application, and shall submit the same to the applicant for the clinical, non-interventional and non-commercial trial, to the Ministry and the Agency.

(2) Within a period of 90 days of the receipt of a correctly filed application, the Central Ethics
Committee shall issue an opinion in writing on the acceptability of the proposed clinical trials of
medicinal products intended for gene therapy, somatic-cell therapy, including also medicinal
products containing genetically modified organisms.

(3) The time-limit referred to in paragraph 2 of this Article may be extended for a further
period of 90 days in the case of the need to consult experts or commissions.

(4) The time for issuing opinions on the acceptability of clinical trials of xenogenic medicinal
products shall not be limited.

Article 15

(1) After receiving a positive opinion from the Central Ethics Committee, the applicant for a
clinical trial, including applicants for non-commercial clinical trials, shall submit a request to the
Ministry for authorisation of the clinical trial in the Republic of Croatia.

(2) The Ministry shall grant or refuse authorisation for the clinical/non-interventional trial
within 30 days from the receipt of a correctly filed request.

(3) The time-limit referred to in paragraph 2 of this Article, may be extended by an additional 30
days for clinical studies relating to gene therapy, somatic-cell therapy, also including medicinal
products containing genetically modified organisms, and xenogenic medicinal products.

(4) Should the Ministry fail to either grant or refuse the authorisation within the time-limits
referred to in paragraphs 2 and 3 of this Article, the authorisation shall be deemed to have been granted, except when the written authorisation of the Ministry has to be obtained before commencing the clinical trials of a medicinal product intended for gene therapy, somatic-cell therapy, also including medicinal products containing genetically modified organisms, and clinical
trials of xenogenic medicinal products.

(5) The Ministry shall refuse authorisation for the clinical trials of medicinal products for
gene therapy if there is a risk of genome alteration in the reproductive cells of the trial subjects.

(6) The Ministry shall grant or refuse authorisation for clinical trials, including non-commercial clinical trials, by adopting a decision, against which no appeal is permitted, but administrative proceedings may be initiated.

(7) By way of derogation from paragraph 1 of this Article, an applicant may simultaneously
submit requests for authorisation of a clinical trial to the Central Ethics Committee and the Ministry.

(8) Applicants for a non-interventional trial shall submit their applications to the Agency.

(9) The Agency is obliged to either approve or refuse the authorisation within 30 days
of the day of receipt of a correctly filed application for conducting the non-interventional
trial.

(10) The Agency shall grant or refuse authorisation for conduct of a non-interventional
trial by adopting a decision, against which no appeal is permitted, but administrative
proceedings may be initiated.

Article 16

(1) Clinical trial applicants are required to inform the Central Ethics Committee and the
Ministry about any significant amendments to a clinical trial.

(2) The Central Ethics Committee and the Ministry shall give their opinions regarding any significant
amendments to the clinical trial within 35 days from receipt of a correctly filed
request.

(3) After receiving the positive opinion of the Central Ethics Committee, the applicant may
introduce significant amendments to the clinical trial if the Ministry fails to inform
them of the reasons for refusing the authorisation within the period of time referred to in paragraph 2 of this Article.

Article 17

(1) Clinical trials of medicinal products shall not be conducted without the informed consent of
the trial subjects.

(2) In exceptional cases, i.e. where a trial subject is unconscious, or suffering from severe
mental impairment, has no capacity to exercise her/his rights, or is a minor, the informed
consent shall be given by their legal representative or guardian, after they have been made
aware of the risks and the objectives of the trial.

(3) The persons referred to in paragraphs 1 and 2 of this Article may, at any time, withdraw their
informed consent to participation in the clinical trial.

(4) Clinical trials shall not be conducted if the potential risks of using a medicinal product
outweigh the medical justification of the trial.

(5) Prisoners or persons who might be coerced into giving consent to participation in a clinical
trial may not be the subject of trials.

Article 18

(1) The principles of medical ethics and the compulsory protection of privacy and information
about the subjects shall be observed when conducting clinical trials, as prescribed by the ordinance
on good clinical practice issued by the Minister.

(2) Clinical trials of medicinal products may only be conducted on the premises of the legal
person referred to in Article 9 of this Act, with whom the applicant or their authorised
representative established in the European Union has signed a clinical trial agreement.

(3) The total costs of the clinical trial and the expenses of the applicant, including the costs of
medical and other services incurred by the legal person referred to in Article 9, as well as
compensation for testers and subjects, shall be defined by the agreement referred to in
paragraph 2 of this Article.

(4) The clinical trial sponsor shall pay the compensation for the testers and trial subjects,
referred to in paragraph 3 of this Article, to the legal person with whom the
clinical trial agreement was signed.

(5) Before the beginning of the clinical trial, the clinical trial sponsors or their authorised
representatives established in the European Union must be insured against liability for any injury,
death, or treatment required by the trial subjects, related to the clinical trial.

Article 19

(1) The Ministry shall enter clinical trial data into the European
database on the following:

- applications submitted for clinical trial authorisation,

- amendments to the applications referred to in subparagraph 1 of this paragraph,

- amendments to trial protocols,

- positive opinions given by the Central Ethics Committee,

- the completion of clinical trials, and

- any supervision undertaken of the observance of good clinical practice.

(2) In addition to the data referred to in paragraph 1 of this Article, the Ministry shall also submit
other information on clinical trials in response to a reasoned request by a Member State,
the EMA or the European Commission.

Article 20

(1) The Ministry may suspend a clinical trial or cancel its authorisation for a clinical trial when, on
the basis of verified facts it determines that the conditions on the basis of which the authorisation
was granted no longer exist, or in the case of any doubt regarding the safety of the subjects or
the scientific value of the clinical trial, and the Ministry shall inform the clinical trial
sponsor or their representative, the Central Ethics Committee, the EMA or the European
Commission of the suspension.

(2) Before making the decision referred to in paragraph 1 of this Article, the Ministry shall
request a written declaration or explanation by the sponsor, or their representative and/or the
tester.

(3) The declaration/explanation referred to in paragraph 2 of this Article shall be provided
within seven days from the date of receipt of the Ministry's request, except in the case of an
immediate and significant risk.

Article 21

In the process of development and manufacture of the medicinal product being tested, while
drafting the documentation related to clinical trials, and in the course of the clinical trials, the
clinical trial sponsors and testers shall comply with the provisions of this Act and
observe the regulations arising from it, as well as the principles and standards laid down in the relevant guidelines of the European Commission or the EMA.