

Based on Article 56, paragraph (4) and Article 120, paragraph (6) of the Medicinal Products and Medical Devices Act of Bosnia and Herzegovina ("Official Gazette of BiH", No. 58/08), at the proposal of the Expert Council of the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, the Ministry of Civil Affairs of Bosnia and Herzegovina adopted

ORDINANCE  
ON CLINICAL TRIALS ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

PART I - INTRODUCTION

Article 1

(Subject of the Ordinance)

(1) This Ordinance regulates the area of clinical trials on medicinal products and medical devices in Bosnia and Herzegovina: the procedure for the conduct of clinical trial on medicinal product and medical device, obligations of the participants in the clinical trial on medicinal product and management of documentation in the procedure for the conduct of the clinical trial. When preparing the clinical trial, there shall be established goals, problems, such as risk-benefit ratio, and there shall be an assurance that the selected solutions are scientifically and ethically justified.

According to the provisions of the Declaration of Helsinki contained in the Annex (VI) of this Ordinance and the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences-CIOMS, clinical trials shall be conducted in compliance with fundamental ethical principles: voluntariness; compliance with the law; respect for the person; benevolence and safety.

(2) Prerequisite for the clinical trial of the preclinical studies which provide sufficient evidence on the acceptable potential harmfulness and possible clinical application of the medicinal product.

(3) Before the trial, it is necessary to determine the ways of monitoring and supervision, as well as standard operating procedures.

Article 2

(Definitions)

The following terms in this Ordinance shall have the following meanings:

- a) Good Clinical Practice is a set of internationally recognized ethical and scientific requirements regarding the quality of designing, conducting, recording and reporting on clinical trials conducted on human subjects, which provide the assurance that the rights, safety and wellbeing of trial subjects are protected, and that the results of the clinical trials are credible;
- b) Documentation of the subject is documentation made in accordance with the plan of a clinical trial and it contains information about the subject collected during the clinical trial;

c) Pharmacogenomics is the study of variations of DNA and RNA characteristics related to the response to a given medicinal product;

d) Pharmacogenetics is a branch of pharmacogenomics and it is defined as the study of variation in the chain sequences of DNA related to the response to medicinal product;

e) Pharmacodynamics is the study of the interaction between the medicinal product and its molecular targets;

f) Genes are functional segments of genetic material that serve as a blueprint for protein synthesis;

g) Genome is the total genetic material of an organism;

h) Institutional Ethics Committee is an independent, advisory body, which duty is to evaluate the justification of a clinical trial, as well as the ability for the conduction of a clinical trial according to the principles of Good Clinical Practice in order to protect the rights, safety and wellbeing of human subjects involved in the clinical trial;

i) Investigator is a person responsible for the conduct of a clinical trial at a trial site;

j) Principal investigator is the investigator responsible for the conduct of a clinical trial on medicinal product if the trial is conducted by a team of individuals (research team);

k) Subject is a person who participates in a clinical trial as a user of a tested medicinal product, medicinal product which is compared to the tested medicinal product or placebo;

l) Report on a clinical trial is a written report on the progress of a clinical trial of any therapeutic, prophylactic, or diagnostic product, which includes clinical and statistical processing of the data, views, analysis and conclusions;

m) Single-blind or double-blind study implies that the candidate does not know what he or she receives, that is, neither the subject nor the investigator, nor the competent observer do not know who received what.

n) Categories of data coding

Single coded data and samples are marked by one specific code and do not include any personal identifiers. In the case of single coding, it is possible to connect the data or samples to a particular person by using the encryption key. Clinical researcher is responsible for the encryption key. Since the samples and accompanying data may be indirectly related to the subject of the research, it is possible to take actions such as withdrawal of samples or return of the individual results at the request of the subject by using the encryption key. Use of the single coded data and samples allows clinical monitoring, monitoring of the subjects or adding the information on the subject. Single coding is the current standard used in clinical trials and it offers an additional guarantee for the identifier of the subject, compared to the general principles of trust in the health care system and the protection of privacy in daily medical practice;

Double coded data and samples are initially marked by one specific code and do not carry any personal information. Afterwards, data and samples are marked by the other code that linked to the first one via the second encryption key. It is possible to connect data or samples to a subject by using both encryption keys. Clinical researcher is responsible for the first encryption key and he or she has no access to the second key. Since the samples and corresponding data may be indirectly related to the subject of the research by using both encryption keys, it is possible to take actions such as withdrawal of samples or return of the individual results at the request of the subject. However, the opportunities to link genotypic result to the subject may be limited by additional electronic or technical processes. For example, certain computer procedure may add new information on the subject to prevent the linking of genotype information with the personal data of the subject. Use of double coded data and samples allows the clinical monitoring, monitoring of the subjects or adding the information on the subject.

Using a second code provides an additional confidence and protection of the subject's privacy, which is greater than with single coding.

It is necessary to have the access to both keys to connect any data or samples with personal information on the subject. Anonymized data and samples are initially single or double coded, but the connection between the personal data of the subjects and the unique code is then deleted. When the connection is deleted it is no longer possible to link data and samples with the people by using the encryption keys. "Anonymization" prevents the identification of the subject. Since the "anonymized" samples and corresponding data may not be linked to the subject, it is not possible to undertake actions such as sample withdrawal or return of the individual results even at the request of the subject. The use of anonymized data and samples does not allow the clinical monitoring, monitoring of the subjects or adding the information on the subject. By deleting the encryption keys which bind the data and samples with personal information about the subject, the additional confidence and privacy is acquired as it prevents re-identification of the subject by using the keys. Anonymous data and samples are never labeled by personal data when they are collected, nor an encryption key is created.

Therefore there is no possibility of linking genomic data and samples with the individual subjects. In some cases, only limited clinical data can be connected with anonymous samples (for example, samples from subjects with diabetes, men, age 50- 55, Cholesterol > mg / dl). Since the anonymous samples and corresponding data may not be linked to the subjects, it is not possible to undertake actions such as sample withdrawal or return of the individual results even at the request of the subject. The use of anonymous data and samples does not allow the clinical monitoring, monitoring of the subjects or adding the information on the subject.

o) Clinical trial is any systematic investigation of a medicinal product intended to discover or verify its effects, and/or to identify any adverse reactions of a medicinal product. Clinical trial includes the clinical part of the study of the bioavailability and bioequivalence of the medicinal product with the object of ascertaining its safety and efficacy;

- p) Final report, report on the completed clinical trial, contained in Annex number (IV) of this Ordinance is a detailed description of the trial after it is completed and includes a description of the description of the methodology of the trial, the method of statistical data processing, a description of the subjects, presentation and evaluation of the results of statistical analysis, and critical, ethical, statistical and clinical evaluation of the entire trial;
- q) Quality control implies the operational techniques and activities undertaken within the quality assurance system, with an aim to confirm the fulfillment of all quality requirements;
- r) Good Manufacturing Practice is part of a quality assurance system that ensures that the medicinal products are consistently and continuously produced and controlled according to appropriate quality standards in accordance with their intended purpose;
- s) Multicenter clinical trial is a clinical trial conducted according to a single protocol for clinical trial in multiple centers, guided by several investigators, whether the centers where the trials are conducted may be located in one or more than one states;
- t) Monitoring is a systematic examination conducted by (usually at randomly selected sample of data) qualified person who does not directly participate in the trial, with an aim to determine whether the relevant clinical trial is conducted according to the approved study plan, in accordance with standard operating procedures and Good Clinical Practice. Supervision is done by a monitor that has the appropriate qualifications for performing monitoring during a clinical trial and has training on Good Clinical Practice;
- u) Competent observer is a qualified person who, on behalf of the orderer of the trial, independently assesses the compliance of all activities associated with clinical trials, the protocol, standard operating procedures, Good Clinical Practice and with the current regulations;
- v) Orderer of the trial is a legal entity which requests the conduction of clinical trials;
- w) Side effect of a medicinal product is every harmful and unintentionally caused reaction that may occur in the therapeutic dose of the medicinal product. Side effect of the medicinal product may also be defined as any adverse reaction to a medicinal product that is applied in the usual dose for prophylactic, diagnostic or therapeutic purposes, or for modification of physiological function, provided that there is a causal relationship, or the connection cannot be excluded;
- x) Adverse reaction to a medicinal product in clinical trial is undesirable and unintentionally induced reaction in patient, which may occur in clinical trial of the medicinal product in connection with any dose of a medicinal product;
- y) Unexpected side effect of a medicinal product is the effect of a medicinal product which nature, severity or outcome are not known and are not described in the summary of the main characteristics of a medicinal product and in the instruction on medical use of medicinal product, and this effect is not part of the current knowledge on the medicinal product;

z) Adverse event in a clinical trial is an unwanted experience (any unfavorable and undesirable sign such as abnormal laboratory results, symptom, or disease in the study) that occurred during clinical trials on medicinal product, regardless of whether there is a causal connection with the use of a medicinal product;

aa) Other documentation on the subject includes medical records, specialist examinations reports and / or specific information about a subject that allow the verification of credibility of the information in the test-lists of subjects and, if necessary, allow the amendment and correction of the same;

bb) Quality assurance of a clinical trial includes systems and quality control procedures which ensure conducting of the trial and obtaining the data in accordance with Good Clinical Practice, including the rules regarding ethical and professional conduct of standard operating procedures, preparing the reports and qualification of professional staff;

cc) Serious side effect of a medicinal product in a clinical trial is undesirable and unintentionally induced reactions to a medicinal product in a clinical trial of that medicinal product, which can cause death, life-threat, disability, hospitalization (which has not been necessary before that), an extension of hospital treatment or congenital anomalies or defects at birth and after birth;

dd) Serious adverse event in a clinical trial is an undesirable experience that occurred during clinical trials of a medicinal product, regardless of whether there is a causal link with the use of a medicinal product, which can cause death, life-threat, disability, hospitalization (which has not been necessary before that), an extension of hospital treatment, congenital anomalies or defects at birth and after birth or the occurrence of malignancy during the trial;

ee) Post-marketing interventional clinical study of a medicinal product is a prospective study in which the medicinal product is administered in accordance with the conditions specified in the marketing authorization, and which requires additional diagnostic procedures, as well as monitoring procedures defined by the protocol on the clinical trial on medicinal product;

ff) Post-marketing non-interventional clinical trial of a medicinal product (pharmacoepidemiological trial) is a study in which a medicinal product is administered in accordance with the conditions specified in the marketing authorization, in which the selection of patients is not pre-determined by the protocol of clinical trial, but it falls within current practice of established treatment, provided that the prescription of a medicinal product is clearly separated from the decision to involve the patient in the study. Further diagnostic procedures or monitoring procedures do not apply, but epidemiological methods are used for the analysis of collected data.

gg) Protocol is a document that describes the objectives, design, methodology, method of statistical data processing and organization of a clinical trial in accordance with Good Clinical Practice;

hh) Consent of a subject is a written statement of a subject, parents of the child, guardian or legal representative, by which he or she voluntarily confirms the willingness to participate in a particular clinical trial after he/she was informed, verbally and in writing, about all aspects of the

trial that are relevant for making a decision on participation. The consent of a subject is documented by signed statement of consent of a subject, containing the date of signing;

ii) Randomization is the process of inclusion of subjects in the therapy or control groups using the method of random selection, in order to reduce bias;

jj) Standard Operating Procedures (SOP) are detailed written instructions for the implementation of every specific situation during the clinical trial, which enable the equal implementation of all functions and activities during the particular clinical trial;

kk) Certificate of Good Clinical Practice- a document which confirms knowledge of Good Clinical Practice;

ll) Raw data are certified copies of original observations, clinical findings and other information about the activities within the framework of clinical trials, which are necessary for the reconstruction and evaluation of the tests. These data include the laboratory records, notes, bills, data obtained through the automated instruments, accurate verified copies in the form of photocopies, photographic negatives, microfilms or magnetic media;

mm) Instructions for the examiner is a document that contains relevant information about the medicinal product, information about the analytical, pharmaco-toxicological testing, as well as about the previous clinical trials of the medicinal product, including data that are important for clinical trials to which they relate. Instructions also include the information that justify the nature, scope and duration of the trial, evaluation of potential harmfulness, special warnings, and they are updated according to new data.

### Article 3

#### (Phases of the clinical trial on medicinal product)

Clinical trial is divided into several phases, as it follows:

a) Phase 1: It represents the first administrations of a medicinal product in humans and it is carried out in order to determine a preliminary assessment of safety and pharmacokinetic / pharmacodynamics profile of the active substance in humans;

b) Phase 2: It includes Phase 2a and Phase 2b;

Phase 2a of a clinical trial represents an early stage of the administration of a medicinal product in a small number of selected subjects who are expected to have useful side effects of medicinal product. It is carried out with the aim of establishing the efficacy and safety of medicinal product, as well as a dose range.

Phase 2b of a clinical trial represents a late stage of the administration of a medicinal product in a large number of selected subjects, with the aim of making a final decision on the dose range and pharmaceutical form. During this phase of the clinical trial, the data collection on the metabolic activity in the human body during the administration of the medicinal product over a longer time period compared to the phase 2a is conducted;

c) Phase 3: It represents the administration of a medicinal product in a sufficiently large number of selected subjects with the aim of determining the efficacy and safety of the examined medicinal product. Sufficiently large number of subjects implies the number of subjects from the accepted protocol of a trial from the professional institution which conducts clinical trials for this phase by which it will evaluate the result;

d) Phase 4: It represents release of a medicinal product in limited quantities which are under control. It is carried out with the aim of monitoring the impact of the drug in terms of limited release in selected professional institutions for clinical trials of medicinal products;

e) Post-marketing phase: It represents the examination of a medicinal product, or the monitoring and collection of additional data on its effectiveness and safety, after getting a permit for placement of a medicinal product on the market.

## PART II - Clinical trial on medicinal product

### TITLE I - Procedure of conducting clinical trial on medicinal product

#### Article 4

(Content and manner of conducting clinical trials of medicinal product)

(1) Clinical trial determines: the effectiveness of the drug, the relationship between beneficial and harmful effects of medicinal product, side effects, bioequivalence and bioavailability;

(2) All clinical trials on humans shall be conducted in accordance with the ethical principles established by DECLARATION OF HELSINKI on the protection of patients' rights (hereinafter referred to as the Declaration of Helsinki) and in accordance with the rules of Good Clinical Practices and this Ordinance;

(3) Medicinal product may be clinically examined after received positive ratings from pharmaceutical-chemical-biological and pharmacological toxicological testing of the drug.

#### Article 5

(Applicant for a clinical trial)

(1) Clinical trials are carried out at the request of the Applicant for a clinical trial: manufacturer, legal or natural persons who act on behalf of manufacturer, which has its headquarters in Bosnia and Herzegovina, interested legal entities, individuals, or at the request of the competent ministry;

(2) Applicant for a clinical trial is responsible for the reliability of the data and information made available to the examiner before the start of clinical trials, or those which are acquired during the trial;

(3) Applicant for a clinical trial and the examiner are obliged to cooperate with an authorized institution which performs clinical trials regarding reporting, implementation of the changes made to protocols of clinical trials, reporting adverse effects and the submission of trial reports;

(4) Applicant for a clinical trial shall organize a system of quality assurance (including independent monitoring) for the conduct of the study;

(5) Applicant for a clinical trial shall prepare detailed written standard operating procedures (SOP),

(6) Applicant for a clinical trial and the examiner shall arrange and sign a protocol of a clinical trial on medicinal product, and determine the method of data entry.

#### Article 6

(Issuance of the approval for clinical trial on medicinal product)

(1) Every clinical trial on medicinal product have to be approved by the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (hereinafter: the Agency);

(2) Before issuing a permit for conducting the clinical trial on medicinal product "mentioned in paragraph (2) of this Article," the Agency shall obtain the agreement of the Committee for clinical trials of medicinal products and medical devices of Bosnia and Herzegovina (hereinafter: the Committee);

(3) The Agency shall issue a permit for clinical trial within 60 days from the day of receipt of the formal and complete application, and based on the opinion of the Committee.

#### Article 7

(The cost of clinical trial on medicinal product)

(1) The costs of registration of a clinical trial and the issuance of permit shall be paid by the applicant for a clinical trial;

(2) The costs of compensation for the work of the members of the Committee are determined by the Agency and paid by the applicant for a clinical trial.

#### Article 8

(Content of the application for clinical trial on medicinal product)

The application for the issuance of a permit for the conduct of clinical trial on medicinal product and medical device shall be accompanied by the following documentation:

a) Cover letter with the mandatory list of documents with the date and signature of those who have submitted documentation;

b) The application form for a permit of clinical trials of medicinal product or medical device which is mentioned in Annex number (I) of this Ordinance and forms its integral part;

c) Information about the sponsor of the study;

w) Letter of authorization of the Contract Research Organization (CRO);

Logo, name and address of the applicant for a clinical trial (logo if any); the name of the expert institution that will participate in the examination, which includes the approval of the Ethics committee of the institution that confirms the participation in the relevant clinical trial;

e) The name of the clinical trial;

f) The name of a medicinal product being clinically examined;

g) The pharmaceutical form and strength;

h) "ATC" - classification, if any;

i) The name of the manufacturer;

j) Evidence of payment of the costs of the proceedings;

k) Explanation of the objective of a clinical trial on medicinal product, indication of the phase of examination and registration status of the medicinal product;

l) Summary of the protocol of a clinical trial in the local language;

m) Plan (protocol) of a clinical trial dated and signed by the principal investigator for the clinical trial;

n) The investigator's brochure in the local language;

o) Proof of insurance of a subject from possible adverse effects caused by participating in a clinical trial on medicinal product and medical device which shall cover the entire period of clinical trial- the local insurance (which shall contain the number of centers and the number of subjects);

p) Current knowledge on adverse effects;

q) Form for reporting serious adverse effects of the medicinal product;

d) List of countries where clinical trials are conducted, including Bosnia and Herzegovina, if it is multicentric;

s) List of countries in which the studied medicinal product is registered;

t) Test-lists of participants "CRP Case Report Form ";

u) Notification for the subject in the local language;

v) Consent form for the subject with a place for the signature of the patient and the principal investigator and a place for a date in the local language;

w) Cards of patients participating in the study;

x) "CV" of the investigator;

y) Proof of education in the field of Good Clinical Practice for the principal investigator.

## Article 9

(Appointment of the investigators for the clinical trial on medicinal product)

- (1) The principal investigator of a clinical trial is a medical doctor or dentist appointed by the applicant for a clinical trial.
- (2) The principal investigator for one calendar year may be appointed for the maximum of three clinical studies.

## Article 10

(Content of documentation for the examined medicinal product)

The documentation for the examined medicinal product includes:

- a) Certificate of Good Manufacturing Practice;
- b) Certificate of the analysis of the medicinal product;
- c) Labeling of the medicinal product;
- d) Proof of conducted pharmaceutical-chemical examination with positive assessment;
- e) Proof of conducted pharmacological-toxicological examination of the medicinal product with positive assessment;
- f) Proof of the registration status of the medicinal product in the country of the manufacturer;
- g) Summary of Product Characteristics and instructions for the use of medicinal product.

## Article 11

(Content of the protocol of the clinical trial on medicinal product)

- (1) Protocol of the clinical trial includes: general information; random selection and "blind" examination and statistical analysis.
  - a) General information include the name of the clinical trial, the identification number and the date. Additions shall have their own number and date. General Information contain the name and address of the applicant for a clinical trial and competent monitor, the names of persons who will sign the protocol of the clinical trial and additions on behalf of the applicant for a clinical trial and investigator who is responsible for conducting the examination, and the name of the institution where the investigation is conducted. Protocol of the clinical trial shall include the aim of the examination, measures that shall be taken to avoid bias, particularly, where relevant, the methods of blind examination and the choice of the subject;
  - b) Method of random selection of a subject shall be documented. When the investigator receives a password for each individual therapy, in the "blind" randomized trial it shall be archived at the site of the examination, and at the applicant for a clinical trial. In the case of a blind examination the protocol of the clinical trial shall include the conditions under which it is allowed to open the

password and name of the person who is authorized to do so. It is necessary to provide a system, which shall, in case of urgency, provide access to information on the treatment of the individual subject. The system shall allow the access to the treatment of one subject at the specific time. If the password is opened, the same shall be justified and documented in the test list of the subject;

c) Types of statistical analysis shall be specified in the protocol of the clinical trial, and any deviation from the protocol of the clinical trial shall be described and justified in the final report on the examination. Planned analysis and its implementation shall be carried out or confirmed and identified by a trained statistician. Opportunities or circumstances of the analysis during the examination shall also be specified in the protocol of the clinical trial. Investigator and authorized monitor shall ensure that the data are of the highest quality that is possible at the stage of their collection, and the statistician shall ensure the unity of data during the processing.

The results of the analysis shall be presented in a way to allow the interpretation of the clinical significance through the assessment of the size of the difference in treatment effect and reliability interval more than just a test of statistical significance. It is necessary to estimate the data that were omitted from the statistical analysis. All such exclusions shall be documented so that another analysis could be conducted if necessary.

(2) Clinical trial shall be carried out in accordance with the protocol of the clinical trial agreed and signed by the applicant for a clinical trial and investigator.

(3) Applicant for a clinical trial and investigator shall agree on any change that occurs during the examination, sign it and add as an addition to the protocol of the clinical trial (amendment).

(4) Protocol of the clinical trial shall contain the aim of the trial, procedures that shall be applied, the reasons why the trial is performed on people, nature and degree of any known risks, the groups from which the subjects shall be chosen and the manners which ensure adequate information before the subject gives the consent to participate in the study.

(5) Model form of protocols for the conduct of clinical trial has determined content in Annex number (II) which forms an integral part of this Ordinance.

## Article 12

### (Content of the instructions for the investigator)

(1) Instructions for the investigator is a brief overview of the existing data of clinical and preclinical studies on medicinal product which is being tested in a clinical trial.

(2) The new information on the medicinal product which are acquired during the clinical trial, the applicant for a clinical trial shall regularly deliver to the investigator in the form of a supplement to the instructions.

(3) Instructions for the investigator include:

- a) Content of clinical trials,
- b) Introductory notes,

- c) Physical, chemical and pharmaceutical characteristics of the pharmaceutical form of the drug and drug formulation,
- d) Pre-clinical trials (pre-clinical pharmacology, pharmacokinetics and metabolism of a medicinal product in animals and toxicology);
- e) Effect of the studied medicinal product on humans (pharmacokinetics, metabolism of a medicinal product in humans, tolerability, effects, and distribution data)
- f) Summary of the main characteristics of the medicinal product and conclusion.

(4) At the end of each part of the instructions for the investigator, it is mandatory to include a list of references which have been used in a clinical trial, and the most important literature shall be attached in a complete form.

### Article 13

#### (Jurisdiction of the Committee)

Upon receipt of the application and documentation for a clinical trial, the Committee shall consider the request, and it shall assess:

- a) Eligibility of the investigator for the proposed trial;
- b) Adequacy of the protocol of the clinical trial in terms of the objectives of the trial and justification of the foreseeable hazards and risks compared to the assumed benefits for subjects and other people;
- c) Way of involving subjects in a clinical trial;
- d) Understandability and completeness of the information given to subjects;
- e) Insurance and compensation in case of death, or in case of the treatment of subjects related to the clinical trial;
- f) Acceptability of the additions to the protocol of the clinical trial.

### Article 14

#### (Principles of voluntary consent of a subject-the Declaration of Helsinki)

During every clinical trial, principles of voluntary consent of a subject have to be applied, in accordance with the provisions of the Declaration of Helsinki, and in particular:

- a) Subject is provided with the information about the clinical trial in oral and written form;
- b) It is not allowed to force subjects to participate in a clinical trial;
- c) Subjects, their relatives, guardians or legal representatives, shall be given the opportunity to acquire knowledge about the details of the trial;
- d) Information "referred to in paragraph (3) of this Article" shall include a clear message that this is a trial, that the participation in a clinical trial is voluntary, and that the subject is free to refuse to participate or to withdraw from the trial;

- e) Subjects shall have enough time to decide whether or not they want to participate in the trial;
- f) Subjects shall be aware of and they shall agree to the verification of test results, and must be aware that the participation in the study is protected as a professional secret and it is accessible to the public as such;
- g) Candidate shall be informed about the insurance and compensation for treatment in case of and of damage or disability caused by participation in the clinical trial;
- h) Subject shall know the circumstances under which the investigator or applicant for a clinical trial may terminate its participation in the study;
- i) Candidate shall be completely informed about the trial, including the aim, expected benefits for the subject or other people, the control treatment / placebo, danger and discomfort (eg, invasive procedures) and, where necessary, interpretation of the accepted alternative standard medical treatment;
- j) If the candidate is unable to give personal consent for the participation in a clinical trial on medicinal product, if he or she is not conscious or is not capable of reasoning, this consent may be given by parents, guardians, legal representatives, spouse, and if the investigator believes that the participation may be useful for the well-being and interests of subject;
- k) If the candidate is a blind person, a deaf person who is not capable to read, a mute person who is not capable to write, or a deaf-blind person, a statement of participation in a clinical trial on medicinal product is given in the presence of one witness.

## Article 15

### (Conditions for conducting clinical trial on juvenile persons)

- (1) If it is necessary, and under special precautions, clinical trial may be conducted on people under 18 years of age who are suffering from a disease or are suffering from a condition for which the medicinal product that is tested is intended.
- (2) Clinical trial on medicinal product which includes juvenile subjects is conducted under the conditions prescribed by law and this Ordinance.
- (3) In addition to the conditions referred to in paragraph (1) and (2) of this Article, Clinical trial that includes juvenile subjects may be conducted if:
  - a) Parent, or legal guardian, has given written consent (written consent shall represent the presumed will of the juvenile and may be withdrawn at any time, without harm to the juvenile);
  - b) Juvenile has been provided the information that are understandable to him or her by a person who has experience in working with juveniles. Those information shall relate to the course of a clinical trial on medicinal product, the risks and benefits to the health of the subject;
  - c) Written consent has been given without the encouragement to participate in a clinical trial on medicinal product by offering or providing any financial incentives or other benefits;

d) Ethics Committee has estimated that the clinical trials on medicinal product conducted on juvenile subject provides a direct benefit to a particular group of patients, and that such research is essential for the evaluation of data obtained by clinical trials on the persons which are capable of giving written consent;

e) Ethics Committee has adopted a positive decision on the implementation of a clinical trial on medicinal product in a medical institution based on the opinion of medical specialist(s) for the area of pediatrics, with special emphasis on clinical, ethical and psycho-social problems in the implementation of a clinical trial on medicinal product.

(4) During the conduct of a clinical trial on medicinal product, the juvenile who is capable of forming an opinion and assess the information received about participating in a clinical trial on medicinal product may decide to withdraw from the clinical trial at any time, and he or she shall inform the principal investigator or other member of the research team.

(5) In the process of approval of a clinical trial on medicinal product which is intended for children, the applicant is obliged to provide the Committee with a positive opinion of the entities` Ministries of health and the Department of Health of Brcko District.

## Article 16

### (Special conditions for clinical trials on adults)

(1) Clinical trial on medicinal product conducted on adult subject who is unable to provide legally valid informed consent (unconsciousness, limited physical or mental ability, etc.), or on adult subject who did not refuse to participate in clinical trial on medicinal product before the beginning of the inability , is carried out under the conditions prescribed by law and this Ordinance.

(2) In addition to the conditions mentioned in paragraph (1) of this Article, clinical trial on medicinal product may be conducted if:

a) Legal representative of the adult subject who is unable to provide legally valid informed consent has given written consent. Written consent shall represent the presumed desire of a subject and may be withdrawn at any time, without harm to the subject;

b) Adult candidate who is unable to give written consent has received information in accordance with their capabilities to understand, by a person who has experience in dealing with such persons, which are related to the course of a clinical trial, the risk and benefit for the health of subjects;

c) Written consent has been given without the encouragement to participate in a clinical trial on medicinal product by offering or giving any material or other benefits;

d) It has been estimated that the clinical trials on medicinal product conducted on that person provides a direct benefit to a particular group of patients whose disease or condition corresponds to the disease or condition of the subject;

e) Ethics Committee has adopted a positive decision on the implementation of a clinical trial on medicinal product in a medical institution based on the opinion of medical specialist(s) for the particular area or state of a subject, and for the population of patients to which the clinical trials refers, with special emphasis on clinical, ethical and psycho-social problems in the implementation of a clinical trial on medicinal product.

(3) During the conduct of a clinical trial on medicinal product, the adult who is not able to give written informed consent, but who is capable of forming an opinion and assess the information received about participating in a clinical trial on medicinal product may decide to withdraw from the clinical trial at any time, and he or she shall inform the principal investigator or other member of the research team.

#### Article 17

(Health protection of the subjects)

Subject shall be provided with the adequate medical care throughout the period of the examination. Health protection shall be provided and after the period of examination, which depends on the nature of the disease, ways of examination and conducted procedures.

#### Article 18

(The site and staff for the clinical trial on medicinal product)

(1) Clinical trial is conducted under conditions that guarantee the security of the subjects.

(2) Selection of the site for clinical trials depends on the degree of the product's development and possible risks that are related to it.

(3) In the case of clinical trials that aim to enter into the genome of subjects in order to achieve pharmacogenomic and pharmacogenetic knowledge, they may be conducted only if the required samples and data provide anonymity or confidentiality.

(4) Site for clinical trials shall have adequate staff, space and equipment, including laboratories.

(5) Research team for the clinical trial on medicinal product that is carried out in a medical institution that provides secondary or tertiary health care shall include medical doctor-specialist in clinical pharmacology, in the case when the first phase of clinical trials on medicinal product is conducted.

(6) During the certain phases of the clinical trial on medicinal product, besides medical doctors and dentists, the research team shall include experts with other relevant qualifications (pharmacists, and specialists in medical biochemistry or specialists in clinical biochemistry, statisticians, nurses, medical technicians, etc.).

## Article 19

### (Multicentric trial on medicinal product)

- (1) In the case of multicentric trial, clinical trial on medicinal product is conducted simultaneously by several examiners, in different locations, based on the same protocol of the clinical trial.
- (2) Multicentric trial "referred to in paragraph (1) of this Article," requires a special administrative system which form depends on the number of the examination sites, end-points of the trial, and the available data on the medicinal product that is being examined.
- (3) Protocol of the multicentric shall contain described functions, responsibilities, and rights and obligations of all participants in the clinical trial.
- (4) In the case of a multicentric trial, it is allowed to establish a coordinating committee or a coordinator with the responsibility to control the practical implementation and the practical progress of the trial and maintain contact with the Agency, expert institution which performs clinical trials, as well as with the other competent authorities in this field.

## Article 20

### (Providing information on the clinical trial on medicinal product)

The applicant for a clinical trial shall regularly inform the Agency and the authorized institution in which examination is being conducted on the course and results of the trial, and that shall be done upon completion of each phase of a clinical trial.

## Article 21

### (Suspension and prohibition of the clinical trial on medicinal product)

- (1) The Agency may during the course of the clinical trial permanently or temporarily stop the clinical trial in the following cases:
  - a) If the Agency finds out that the requirements set out in the Act, in this Ordinance or in the application for the license or permit for the clinical trial on medicinal product are not fulfilled;
  - b) If it is required by the safety of the subject or the protection of health;
  - c) If the principal investigator, other investigator or any other person involved in the approved clinical trials do not fulfill the defined obligations and are not governed by the principles of Good Clinical Practice;
  - d) According to the final and executory decision of the pharmaceutical inspector.
- (2) Agency issues the decision on the suspension or prohibition of further conduct of clinical trials after obtaining the opinion of the Committee. The solution referred to in paragraph (2) of this Article is finally in the administrative procedure.

## Article 22

(Explanation of the early completion of the clinical trial on medicinal product and the final report)

(1) If the clinical trial is completed before the time period specified in the protocol of the clinical trial, the investigator shall submit an explanation of the early termination of the trial to the Agency and professional institution where the clinical trial has been performed.

(2) After the examination is completed, the final report is being prepared. The report referred to in paragraph (2) of this Article, with the exact date of the completion of the clinical trial, shall be signed by the principal investigator and submitted to the Agency and professional institution where the clinical trial has been performed.

## Article 23

(Final Report)

(1) Final report on the clinical trial on medicinal product contains:

a) General information;

b) Protocol, phases and standard operating procedures for the implementation of technical examination according to Good Clinical Practice;

c) Results of the examination which include:

1. Clinical pharmacology (pharmacodynamics, pharmacokinetics, interactions)
2. Bioavailability / bioequivalence,
3. Clinical efficacy and safety,
4. Information on the application of the medicinal product in countries where there is a permission for marketing authorization.

(2) Content of the form for the final report on the conduct of clinical trial on medicinal product is prescribed in Annex number (IV) and it is an integral part of this Ordinance.

## TITLE II - OBLIGATIONS OF PARTICIPANTS IN THE PROCEDURE OF THE CLINICAL TRIAL ON MEDICINAL PRODUCT AND DOCUMENT MANAGEMENT

### Article 24

(Obligations of the applicant for a clinical trial)

The applicant for a clinical trial is required to:

a) Make the selection of investigators taking into account the site of the trial, the equipment and the credibility of the qualifications of the investigators, as well as the duration of the trial;

- b) Inform the investigator about the chemical, pharmaceutical, toxicological, pharmacological and clinical data on the medicinal product (including previous and simultaneous examinations) in accordance with the nature, scope and duration of the examination as a condition of planning the examination, and provide the investigator with all new significant information and data about the medicinal product that appear during the trial;
- c) Submit the application with all necessary documents to professional institution which performs clinical testing;
- d) Provide and deliver the appropriate marked and appropriate coded medicinal products prepared for examination in accordance with the principles of Good Manufacturing Practice and appropriately packaged in a manner that protects the product from damage, provided that the blindness of the procedure is insured;
- e) Preserve enough samples of each batch and the data on the completed analysis and characteristics of the product to be examined so that, if necessary, they may be re-examined by an independent laboratory;
- f) Provide the investigator with the possibility to establish a system for the proper and safe handling, storage, privacy, return and destruction of the examined medicinal product in his or her institution, and to appoint a person responsible for carrying out these activities;
- g) Determine and provide the relevant training for the competent observer;
- h) Determine the persons to monitor the process, and verify the statistical analysis and write the report on the examination;
- i) Consider all the side effects together with the investigator, without delay, and take the appropriate measures necessary for the safety of subjects, and deliver the report on side effect to the Agency;
- j) Ensure the preparation of the complete final report on clinical trial;
- k) Ensure the adequate compensation for the treatment, and treatment for the people in case of damage or death associated with the examination except for those cases that are a consequence of unconscientious action or negligence.

## Article 25

(Special obligations of the applicant for a clinical trial)

- (1) In addition to the obligations referred to in Article 24 of this Ordinance, the applicant for a clinical trial shall ensure the supply of the medicinal product that is examined (product to be examined or reference product, including placebo) so that they are of appropriate quality and subjects to quality assurance procedures.
- (2) Manner in which the applicant for a clinical trial supplies the investigator with medicinal products that are being examined shall be described in the protocol of the clinical trial.

(3) Applicant for a clinical trial supplies the investigator with the medicinal product after he or she receives the necessary permit for the clinical trial issued by the Agency and approval for import issued by the entities` Ministries of health.

(4) When delivering medicinal products referred to in paragraph (3) of this article, the applicant for a clinical trial is required to provide the investigator with written instructions on handling and storage of those medicinal products, as well as the instructions on handling the unused remains after the trial is over.

(5) Applicant for a clinical trial is obliged to prepare a written statement on the delivery of medicinal products, as well as on written instructions referred to in paragraph (4) of this Article.

(6) Applicant for a clinical trial shall ensure the stability of the examined medicinal product as well as a regular supply of medicinal product throughout the study.

(7) Applicant for a clinical trial shall describe in detail the manner in which the examined medicinal product shall be marked, delivered, distributed and preserved.

(8) Notes shall include information on transportation, delivery, receipt, distribution, return and destruction of any remaining medicinal product. Investigator shall not administrate the examined medicinal product to the person who is not designated to receive it.

(9) Applicant for a clinical trial is responsible for the proper packaging and labeling of the medicinal products that are being examined. The label shall indicate that the product is intended only for a clinical trial.

(10) In blind trials packaging must be labeled in a manner that prevents recognition of the identity. Determination of the identity of the current treatment received by a particular subject shall be enabled in emergency situations.

(11) In blind trials the examined medicinal product, including a control drug and placebo, shall have the same appearance, taste, smell and other physical characteristics.

(12) Applicant for a clinical trial is required to ensure that the packaging of the examined medicinal product has the adequate dimensions for the examination and for the subjects, and the applicant is required to provide sufficient samples of each batch for the purposes of re-analysis and control in the future.

(13) If the formulation of the control medicine is changing, the need for the comparative in vivo biological tests and solubility and dissolution test or other in vitro tests should be considered.

## Article 26

### (Observer of the clinical trial on medicinal product)

(1) Competent observer is determined by the applicant for a clinical trial with the consent of the investigator. Number of competent observers depends on the complexity of the trial on medicinal product and the number of centers that participate in it. The competent observer must be available to the investigator.

(2) Primary obligation of the competent observer is monitoring the conduct of the trial and ensuring the implementation of the same in accordance with the protocol of the clinical trial.

(3) Any unjustified digression from the protocol of the clinical trial and any breach of Good Clinical Practice competent observer shall, without delay, inform the applicant for a clinical trial, the Agency and professional institution which performs the clinical trial.

#### Article 27

(Special obligations of the observer of the clinical trial on medicinal product)

(1) In addition to the basic obligations referred to in Article 26 of this Ordinance, competent observer has the obligation to:

a) Monitor the implementation of the protocol of the clinical trial and to ensure that all data in the study are properly and completely recorded;

b) Determine whether the adequate space, staff and equipment, laboratories are ensured for conducting the trial, and to assess the availability of an adequate number of subjects during the examination;

c) Ensure that the staff that assists the investigator during the examination is informed about the trial, and to comply with all the details of the trial;

d) Provide connectivity between the investigator and the applicant for a clinical trial during the conduction of the examination;

e) Ensure that the test lists of the subjects are properly filled;

f) Examine whether the supplies, distribution and recall of the medicinal product that is being examined are insured, and that they are documented in an appropriate manner in accordance with the regulations;

g) Submit a written report to the applicant for a clinical trial after each visit and after any other contact with the investigator.

(2) While visiting the investigator, competent observer shall check:

a) Whether the medicinal product that is being examined is used exclusively for purposes specified by the protocol of the clinical trial;

b) That there are data on the quantities of the medicinal product that is being examined;

b) Expiry date of the medicinal product;

c) Storage conditions of the medicinal product that is being examined;

d) Procedure conducted on returned or unused medicinal products.

## Article 28

(Side effects, adverse reactions and adverse events during the clinical trial on medicinal product)

- (1) Occurrence of any side effects, adverse reactions or adverse events caused by medicinal product should be carefully monitored and recorded in detail during the entire trial.
- (2) Protocol of the clinical trial shall determine a method that shall be used for monitoring of the side effects, adverse reactions or adverse events referred to in paragraph (1) of this Article.
- (3) Applicant for a clinical trial should provide the Agency with questionnaires for reporting of adverse reactions.
- (4) Applicant for a clinical trial shall report any side effects caused by medicinal product to the Agency and the Ethics Committee of the institution which performs the clinical trial.
- (5) Reports referred to in paragraph (4) of this Article shall include the assessment of causal relationship and the possible impact on the trial and the future use of the product that is being examined, as well as the identification of the subject and the methods of examination.
- (6) After finishing the examination, all the recorded side effects caused by medicinal product or medical device shall be determined and assessed in the final report.
- (7) Applicant for a clinical trial is obliged, without delay, to inform the investigator about any examination of the same medicinal product that has been interrupted at any time or place, as well as about the withdrawal of the medicinal product from the market because of lack of safety.

## Article 29

(Notes and data during the clinical trial on medicinal product)

- (1) Aim of keeping the notes during the clinical trial on medicinal product is the registration of information, the transmission of information, effective and regular transformation of information obtained from the subjects into the data that may be used in the report. All the procedures conducted during the trial shall be documented.
- (2) Main characteristic of the uniqueness of data is the insurance of "blind" examination in terms of determining the type of treatment, which begins with the randomization of subjects into different groups, and it is maintained during the entire data processing up to the decision on opening the password.
- (3) In the case of electronic data processing, the secrecy of database, as well as their accuracy, shall be separately insured.

## Article 30

(Method and deadline for keeping the documentation of the clinical trial on medicinal product)

- (1) Applicant for a clinical trial shall ensure the archiving of identification passwords of subjects for safety and efficiency reasons.
- (2) Applicant for a clinical trial shall take appropriate measures for keeping the other documentation relating to the trial.
- (3) Data referred to in paragraph (2) of this Article may be stored on microfilm or electronically, provided that there is a copy on paper.
- (4) Applicant for a clinical trial shall keep the protocol of the clinical trial, documentation, license and any other documents concerning the examination, including certificates of the method of implementation of procedures for 5 years from the completion of the clinical trials, or after the specified period if other applicable criteria or agreements between the applicant for a clinical trial and investigator require so.

## Article 31

(Obligations of the investigator)

- (1) Investigator is responsible for the strict implementation of the protocol of the clinical trial, as it follows:
  - a) The investigator shall not make any changes to the approved trial, except for immediate procedure if it is necessary to eliminate the obvious immediate risk or danger for subjects with obligatory notification of the Agency about it;
  - b) In the case of annexes to the protocol of the clinical trial, it is necessary to obtain the prior approval of the Committee;
  - c) Form of the annexes to the protocol regarding the conduction of the clinical trial on medicinal product has prescribed content in Annex number (III) and it is an integral part of this Ordinance;
  - d) Investigator shall provide adequate information to the subjects in a clinical trial, and respect the provisions of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects;
  - e) Nature of the information that should be presented to the subjects depends on the complexity of the clinical trial and the type of medicinal product that is being examined;
  - f) Information referred to in item e) of this paragraph is generally given orally and in writing and in a language that is understandable to the subject;
  - g) Investigator is obliged to inform the subjects about their participation in the clinical trial, mark the persons from which they may seek assistance in emergency situations, and draw attention to the need to keep mentioned notification with them;

- h) Investigator shall be aware of the characteristics and effects, including information obtained before the clinical trial on the product that is being clinically examined;
  - i) Investigator has to know all the new relevant product information that appear during the conduction of the clinical trial;
  - j) In the case of serious adverse effects, the investigator shall without delay notify the applicant for a clinical trial, professional institution which performs clinical trial and the Agency;
  - k) Investigator shall be available during the periodic visits conducted by competent observer, and during the inspection conducted by pharmaceutical inspector, as well as the person who was nominated by the applicant for a clinical trial to secure the quality of the trial.
- (2) Investigator shall ensure:
- a) Safe procedure with the medicinal product that is being examined during and after the conduct of the examination;
  - b) That the medicinal product that is being examined is only used in accordance with the protocol of the clinical trial, and that the trial involves subjects who are responsible to the investigator;
  - c) That the dose and instructions for use are appropriate, and that every subject may understand them;
  - d) That the unused medicinal product that is being examined is returned to the applicant for a clinical trial or destroyed, and that the records of these activities are kept in accordance with the protocol of the clinical trial.

## Article 32

### (Obligations of the applicant for a clinical trial)

- (1) Applicant for a clinical trial is responsible for the implementation of a system that would ensure quality of verification of the site where the examination is being conducted, all the data and files that are related to it.
- (2) All the observations and findings shall be available to inspection to ensure the authenticity of all data, and to ensure that the conclusions resulting from the processing of the obtained raw data are accurate.
- (3) Verification procedures shall be justified and specified.
- (4) Sampling should be controlled by statistically acceptable method of inspecting the examination.
- (5) Quality control shall be applied at every stage of data processing, to ensure that all data are safe and adequately processed.

## PART III – CLINICAL TRIAL FOR MEDICAL DEVICE

### Article 33

(Purpose of the clinical trials for medical devices)

Examination of a medical device is done for the purpose of determining or confirming the efficacy, safety and quality, in accordance with the declared application specified by the manufacturer.

### Article 34

(Classes of medical devices and the clinical trial)

(1) Clinical trial for a medical device presents the determination or confirmation of harmlessness of a medical device, its effectiveness and compliance with the general and specific requirements according to the purpose specified by the manufacturer.

(2) Clinical trial is conducted for the medical device that belongs to Class IIa, IIb and Class III, while the clinical trial is not conducted for class I, except for the medical device which is sterile, or the one which contains a radiation source.

(3) For the clinical trial referred to in paragraph (2) of this Article, the license is issued by the Agency.

(4) Process of the clinical trial for medical device shall correspond to the contemporary scientific and technical achievements and the principles of Good Clinical Practice in clinical trials and medical ethics. Results of the clinical trial shall include the results of all available clinical trials for medical devices, either positive, or negative.

(5) Documentation of the clinical trial for medical device shall include the results of the examination that are detailed and objectively described and available for enabling of the objective assessment of the benefit-risk ratio in patients, the assessment of its safety, efficacy and opinion on whether that medical device corresponds to the general and specific requirements of the Act and the purpose specified by the manufacturer.

### Article 35

(Content of the application for the clinical trial for medical devices)

(1) Besides the application for a license for conducting the clinical trial for medical device, the following documentation indicated in Annex number (V) which is an integral part of this Ordinance shall be attached:

a) Plan of the clinical trial, which contains goals, methods, control system, organization and method of statistical processing;

b) Proof of insurance in case of any damage to the person or persons who are subjects to the examination, or examination participants, occurred as a result of the examination;

- c) Written consent of the subjects;
  - d) Report on the harmful or adverse effects of a medical device (if any);
  - e) Copy of the study plan of the medical device in the official languages;
  - f) Data on the medical device: name, type, model, label, size;
  - g) Documentation relating to the input materials;
  - h) Documentation relating to a process of production of the medical device;
  - i) Documentation relating to the final product in connection with the intended use and the risk;
  - j) Proposal for labeling of a medical device and instructions for use;
  - k) Documentation or certificate of compliance with the general and specific requirements;
  - l) Documentation of previous clinical trials (if any);
  - m) Short biography of the principal investigator;
  - n) Proof of payment of costs for the application and a license for the clinical trial.
- (2) Agency may require additional documentation if it concerns the safeguarding of public health.

#### Article 36

##### (Jurisdiction of the Agency)

- (1) If the applicant for the clinical trials for medical device does not receive a negative response from the Agency within 30 days from the day of submission of the application, it is considered that the clinical trials for medical device may begin.
- (2) If the clinical trial is denied, the Agency is required, no later than 30 days after receipt of a complete application for a license for the clinical trial of medical device, to issue a decision with the reasoned grounds on which the request is denied. The decision is final in the administrative proceedings and no appeal may be filed against it, but an administrative dispute may be filed at the competent court.
- (3) Deadline referred to in paragraph (2) of this Article shall end on the day when the Agency requests the necessary additional information or explanations from the applicant for a clinical trial, and the termination of the deadline lasts until all the requirements of the Agency are fulfilled.
- (4) Agency may, in order to protect the health of the population, determine the temporary or permanent cessation of the clinical trial.
- (5) Agency may determine control over the conduct of the clinical trial for medical device and respect of the principles of good practices in clinical trial in accordance with the Act.

## Article 37

(Conditions for conduction of the clinical trial for medical device on certain persons)

- (1) Clinical trial for medical device may be conducted only with the written consent-consent of the person on which the trial is conducted.
- (2) Clinical trial for medical device on children may be done only if the trial conducted on adults may provide adequate results.
- (3) In exceptional cases, a person who is unconscious, has severe mental difficulties, is incompetent to work or is a minor, the written consent is provided by the legal representative or legal guardian of the person.
- (4) Clinical trial shall not be conducted if the possible risks of the use of a medical device is higher than the medical justification of the examination of a medical device, as assessed by the Committee or the Director of the Agency.
- (5) Clinical trial shall not be conducted on prisoners or persons who might be coerced into giving the consent to participate in a clinical trial for medical device.

## Article 38

(Costs and persons authorized to apply for the clinical trial for medical device)

- (1) Prior to the commencement of the clinical trial for medical device on the territory of Bosnia and Herzegovina, the intended clinical trial for medical device should be reported to the Agency.
- (2) Applicant for the clinical trial for medical device may be a sponsor, manufacturer, or importer, or, on their behalf, the principal investigator of the clinical trial for medical device.
- (3) Costs of the clinical trial and consideration of the application for clinical trial for medical device shall be paid by the applicant for the clinical trial.
- (4) Agency or entities` Ministries of health and the Department of Health of Brcko District, another state or entity`s ministry or some other legal entity, may request the clinical trial for medical device for the purpose of protection of public health.
- (5) Costs of the trial shall be paid by the applicant for the clinical trial only if it is proven that the safety, effectiveness and compliance of the medical device with the general and specific requirements correspond to the provisions of the Act and regulations based on the abovementioned.
- (6) If it is proved that the safety, efficiency and compliance of the medical device with the general and specific requirements do not correspond to the provisions of the Act and regulations based on the abovementioned, the cost of clinical trial shall be paid by the manufacturer or importer of a medical device.

## Article 39

(Amendments, final report and notification on the clinical trial for medical device)

- (1) Manufacturer shall submit to the Agency all additions or changes to the already approved plan of the clinical trial for medical device.
- (2) Report signed by the principal investigator, shall contain critical evaluation of all the data obtained and collected during the clinical trial for medical device.
- (3) Applicant for the clinical trial shall notify relevant authorities of the interested member states about the completion of the clinical trial for medical device, and in the case of premature termination notification shall be accompanied by the justification.

## PART FOUR - FINAL PROVISIONS

### Article 40

(Amendments to the Ordinance)

Amendments to this Ordinance shall be conducted in a manner of and according to the procedure for its adoption.

### Article 41

(Cessation of validity of the regulations)

With the entry into force of this Ordinance, the Ordinance on Good Clinical Practice and clinical trials on the medicinal product ("Official Gazette of the Federation of Bosnia and Herzegovina", no. 61/04), the Ordinance on amendments to the Ordinance on Good Clinical Practice and clinical trials on the medicinal product ("Official Gazette of the Federation Bosnia and Herzegovina ", no. 56/05), the Ordinance on clinical trial on medicinal product (" Official Gazette of the Republic of Srpska ", no. 64/05) and Ordinance on amendments to the Ordinance on clinical trial on medicinal product (" Official Gazette of the Republic of Srpska" no. 23/07).

### Article 42

This Ordinance shall enter into force on the day of granting and shall be published in the "Official Gazette of BiH".

Number 08-02-2-1172-2-JD / 09

Minister

Date: December 10<sup>th</sup>, 2009

Mr. Sredoje Novic, s.r.