REGULATION
OF THE CONDITIONS AND THE ORDER FOR CONDUCTING CLINICAL TRAILS WITH DRUGS ON HUMAN SUBJECTS

Chapter 1
Part I

Article 1

(1). This regulation defines:

1. The conditions and the order for conducting clinical trials with drugs on human subjects in compliance with the Principles of the Good Clinical Practice (GCP) stated in the Guideline for Good Clinical Practice (GGCP), application 1.

2. The conditions and the order of work for the Local Ethics Committee (LEC), Specialized Committee for Approving Clinical Trials of Drugs, and the Central Ethics Committee (CEC).

(2). All phases of the clinical trials, including testing of bioavailability and bioequivalence, shall be designed, conducted and reported in compliance with the Principles of the Good Clinical Practice

Chapter 2.

Approvals of Conducting a Clinical Trial

Article 2.

For conducting a clinical trial of a drug the principle investigator, and the sponsor or his/hers legal representative shall present in the Local Ethics Committee in the medical institution where the trail is going to be conducted, the following documents:

1. A Study protocol of the clinical trial written in compliance with the Good Clinical Practice

2. An Investigator's Brochure written in compliance with the Good Clinical Practice

3. Case Report Form of the patient /volunteer.

4. Documents showing compliance with the requirements of the Law of Drugs and Pharmacies in Human Medicine (LHPHM) , article 42, paragraph 1

5. Insurance policies for the patient/volunteer and the investigators.

6. A project for written informed consent of the patient /volunteer in Bulgarian language.

7. A project for written information for the patient /volunteer in Bulgarian language concerning the essence, significance, scope and the potential risks of the study.

8. A document showing that pharmaco-toxicological studies are conducted in compliance with the Good Laboratory Practice – in the case of multi-center trial.

Article 3.

(1). In one month period after the documents in Article 2 are submitted, the Local Ethics Committee shall approve the plan and give a motivate decision if the plan is in compliance with the Principles of Ethics, and is in compliance with the Good Clinical Practice.

(2). In case that the Local Ethics Committee does not approve the plan, the sponsor may ask for a new approval of the plan with the Central Ethics Committee.

Article 4.
(1) For receiving an approval for conducting a clinical trial of a drug in the cases stated in Article 37, par. 1, point1 in LDPHM, the principle investigator and the sponsor or his/hers legal representative present in the Bulgarian Drug Agency (BDA) the following documents:

1. Three copies of a notification form in compliance with the application 2. The document shall be filled in Bulgarian language and shall be signed by the principle investigator and the sponsor or his/hers legal representative.

2. The approved Study protocol of the clinical trial by the Local Ethics Committee.

3. All documents needed in compliance with Article 2, points 2-9

4. The decision from Article 3 by the Local Ethics Committee

5. An invoice for the paid the state fee in compliance with the Rates of Taxes of the Ministry of Health according to Article 8, par 1 in LDPHM.

6. A preliminary specification of the medicinal substance and the medicinal product or relevant data for compliance with the standardization documents as approved in Art. 37, par. 1 in LDPHM

7. A document that the batches allocated for the clinical trial are representative for manufacturing process.

8. A document of legal representation of the sponsor in case when documents shall be submitted by a legal representative.

9. Documentation for country registration of the Contract Research Organization in case that one is appointed in the clinical trial.

Article 5.
For starting a clinical trial in the cases of Art. 37, par 1, point 2 in LDPHM, the principle investigator and the sponsor or his/hers legal representative shall present in the Bulgarian Drug Agency the following documents:

1. Three copies of notification form in compliance with the application 2. The document shall be filled in Bulgarian language and shall be signed by the principle investigator and the sponsor or his/hers legal representative.

2. The approved project of the protocol of the clinical trial by the Local Ethics Committee.

3. All documents needed in compliance with Article 2, points 2-7 and 9

4. The decision under Article 3 by the Local Ethics Committee

5. An invoice for the paid state fee in compliance with the Rates of Taxes of the Ministry of Health according to Article 8, par 1 in LDPHM.

6. A document that the batches allocated for the clinical trial are representative for manufacturing process.

7. A document of legal representation of the sponsor in case when documents shall be submitted by a legal representative.

8. Documentation for country registration of the Contract Research Organization in case that one is appointed in the clinical trial.

Article 6.

When any discrepancies or incompleteness in the presented documents in Art. 4 and 5 are detected, the Bulgarian Drug Agency shall send a written notification to the applicant and shall give instructions for correcting them. In such cases the period stated in Art. 7, par. 1 and Art. 8, par. 1 is stopped from the day of the notification to the day when the discrepancies or incompleteness are corrected. The procedure of approving the clinical trial is discontinued in case that the applicant does not correct the discrepancies or incompleteness in three months period after the written notification.

Article 7.

(1). Within two months of the submission of the documents in Art. 4 for conducting a clinical trial according to Art. 37, par.1, point 1 in LDPHM, the Specialized Committee for Approving the Conduct of Clinical Trials shall issue an approval for conducting the clinical trial or shall give a motivate refusal.

(2). A copy of the document of approval or refusal is forwarded to the Local Ethics Committee, the sponsor, and the Bulgarian Drug Agency.

Article 8.

(1). The conduct of a clinical trial under Art. 37, points 1and 2 in LDPHM may initiate if the applicant does not receive a rejection by the Executive Director of the Bulgarian Drug Agency in a term of one month after the submission of the documents under Art.4

(2). No approval shall be granted in case of discrepancies in the documents with the Guidelines of the Good Clinical Practice published in the Guideline of Good Clinical Practice – application 1.

(3). In case of refusal under the previous point the Bulgarian Drug Agency sends immediately a copy of the refusal to the sponsor and the principle investigator.

Article 9.

(1). Documents for a new approval shall be submitted in case of changes in:

1. The composition of the drug
2. Dosage form
3. Drug application
4. Medicinal form
5. Therapeutic group of patients

(2). For all other changes in the clinical trial the sponsor or his/hers legal representative should notify the Local Ethics Committee and the Bulgarian Drug Agency during the clinical trial.

Chapter 3

Responsibilities of the Sponsor and the Principle Investigator

Article 10.

(1). The sponsor guarantees the quality and the control in the conducting of a clinical trial and presents reliable results from the trial.

(2). The sponsor can assign a Contract Research Organization and transfer all or part of his responsibilities.

(3). All contracts between the sponsor and other people shall be in written form and shall be a part of the plan or of another separate part.

(4). The sponsor shall insure the patients/volunteers and the investigators for the cases of affecting the health or death during the conduct of the clinical trial

(5). The sponsor shall prepare labels for the studies medicine in an easy and understandable language for the investigators and the patient/volunteer. The labels shall contain:

1. Code of the investigational drug
2. Quantity in one package
3. Batch number
4. Expiry Date
5. Notification that the product will be used for a clinical study purpose only.

(6). The sponsor shall keep all the original documents of the clinical trial and the identification codes of the patients for the period stated in the Guideline for Good Clinical Practice

Article 11.

(1). The sponsor presents a report of the clinical trial to the Bulgarian Drug Agency in the period of one year after the end of the clinical trial

(2). The sponsor keeps the report under Art. 9 for the period stated in the Guideline of Good Clinical Practice – application 1.

Article 12

The principle investigator:

(1). Follows the approved protocol for conducting the clinical trial. Changes from the approved plan may be made only in serious cases such as affecting the health, the life, and the rights of the studies human subjects.

(2). Provides the sponsor all the original documents from the clinical trial after the trial is over.

(3). Returns to the sponsor the unused qualities of the medicine.

(4). Keeps copies of the documentation according to the approved protocol, the hospital documentation, and the informed consent forms for the period of at least 15 years after the end of the trial.

Article 13
(1). The sponsor and the principle investigator shall notify the Bulgarian Drug Agency for all serious and unexpected events in the country during the clinical trial in the following periods:
1. The sponsor in the period of 15 calendar days after receiving the notification, and in the period of 7calendar days in the case of death.
2. The Principal Investigator in the period of 15 calendar days after occurrence, and in the period of 7calendar days in the case of death.

(2). When the clinical trial is conducted in other countries also, the sponsor is obliged to notify the Bulgarian Drug Agency for all serious and unexpected medicinal reactions, as well as for the precautions of the regulatory taken in those counties.

Article 14.
The Principle investigator and the sponsor are obliged to notify the Bulgarian Drug Agency in the cases of not starting the clinical trial or in the cases of premature termination. In both cases reasons for the taken action should be given.

CHAPTER II
Part One
Conditions and Order of Work of the Local Ethics Committees

Article15
(1). Local Ethics Committee is established in the same medical center where the clinical trial is going to take place.

(2). The chairman or a member of the Local Ethics Committee can be assigned for two following mandates in the same committee.

(3). Each mandate continues for two years.

(4). Each member or a lecturer of the Local Ethics Committee should declare in a written form whether he/she works as a consultant or holds another office with the sponsor.

Article16
(1). Local Ethics Committee reviews and estimates the scientific, medical, and ethical aspects of the given clinical trial and gives a motivate decision.

(2). Local Ethics Committee performs a periodical review of each clinical trial during its conduct on a certain periods of time, depending on the risks for the patients/volunteers. These reviews should not be less than once per year.

(3). If necessary, the Local Ethics Committee may ask for more information concerning the safety of the patients/volunteers in the trial.

Article 17
(1). The Local Ethics Committee defines its functions in compliance with the Good Clinical Practice and also with the written standard operating procedures, written by the committee.

(2). The Standard Operating Procedures of the Local Ethics Committee should be written in compliance with the Guideline of the Good Clinical Practice and are approved by the Executive Director of the Bulgarian Drug Agency.

(3). The Bulgarian Drug Agency controls the adherence of Local Ethics Committee to the Standard Operating Procedures.

(4). The Local Ethics Committee consists of at least seven members. At least one of the members should be without medical education and at least one member should be financially and administratively independent from the medical center.

Article 18
(1). The meetings of the Local Ethics Committee are open to the public.

(2). The meetings of the Local Ethics Committee are legal if 2/3rds of the members are present.

(3). The Local Ethics Committee shall take decisions by the majority.

(4). During the meetings only the members who are financially and administratively independent from the principle investigator and the sponsor and who do not participate in the clinical trial may give opinions or vote.

Article 19.
The Local Ethics Committees provide the Central Ethics Committee with an annual report on its practice.

Part II

Conditions and Scope of Work of the Specialized Committee for Approval Conducting of Clinical Trials (SCACCT)

Article 20.
SCACCT:
1. Reviews and gives an approval/motivate refusal for conducting clinical trials with non-permitted drugs in the country.

2. Reviews and issues an approval/motivate refusal for any changes in the plans of already approved clinical trial.

3. Reviews and issues a statement on the basis of results on conducted clinical trials on the territory of the country.

Article 21.
SCACCT defines rules for its activities, which are accepted at a regular meeting.

Article 22.
The meetings of the SCACCT are held no later than one month from the submission of the documents in Bulgarian Drug Agency.

Article 23.
For his activities the SCACCT can consult with independent experts.

Article 24.
SCACCT makes the decision/ motivate refusal in seven days after the meeting.

Part III

Conditions and Order of Work of the Central Ethics Committee (CEC)

Article 25.
CEC issues a decision of the ethical aspects of the clinical trials when it is approached by the Minister of Health, Specialized Committee for Approval of Clinical Trials, Bulgarian Drug Agency, Local Ethics Committees and from the sponsor in the case of non-agreement with the decision of the Local Ethics Committee.

Article 26
The Central Ethics Committee issues its statement in compliance with the provisions of the constitution, the Law of Drugs and Pharmacies in Human Medicine, the international agreements for protection of human rights, to which Republic of Bulgaria is a party.

Article 27.
The Central Ethics Committee defines the rules for its activities, which are approved during regular meetings.

CHAPTER III

Control on the Conducting of Clinical Trials

Article 28.
(1). The defined in article 91 (3) in LDPHM state inspectors perform control on the clinical trials, conducted in the Republic of Bulgaria.

(2). The control conducted by the state inspectors is current and final. Objects of the control are the sponsor, the principle investigator and investigators, as well as the whole documentation on the clinical trial.

Article 29. The control on the clinical trial is conducted in compliance with the Standard Operating Procedures, approved by the Director of Bulgarian Drug Agency.

Article 30.
The Bulgarian Drug Agency keeps the information on the conducted in the country clinical trials.

Additional Decree

§ 1. On the basis of this law:

1. Study of bioavailability is a clinical study, which purpose is to show what are the speed and the degree at which the medicinal substance or the therapeutic essential part of the tested drug reach a pharmaceutical form in the system blood circulation.

2. Study of bioequivalence is a clinical study, which purpose is to show that two medicines are bioequivalent if they are pharmaceutically equivalent or represent alternatives and when their bioavailability after being used in the same molar dosage are similar to a degree which is a condition for equivalent efficacy and safety.

3. Adverse event is every unfavorable and unintended sign (including abnormal laboratory finding), symptoms or a disease temporarily associated with the use of a medicinal (investigational) product, whether or nor related to the medicinal (investigational) product.

4. Serious adverse reaction is any untoward medical occurrence that at any dose
- Results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect.

5. Contract Research Organization is an organization (business, scientific, or other), contracted by the sponsor to perform one or more of a sponsor's trial related duties and functions.

6. Trial Center is the location where trial-related activities are actually conducted.

Final Decree

I. This law is published on the basis of article 21, art. 37, (4), art. 40,1, art. 44 in LDPHM

II. This law cancels Law #14 of the Ministry of Health from July 22, 1996 "For the Conditions and the order of Conducting Clinical Trials on Human Subjects" (SG, #70, 1996) and Law #26of the Ministry of Health from August 3rd, 1995 " To determine the structure, the conditions and the order for the work of the Central Ethics Committee" (SG, #72, 1995)