REGULATION

From the Ministry of Health:

REGULATIONS REGARDING CLINICAL TRIALS

SECTION ONE

Objective, Scope, Legal Basis and Definitions

Objective

ARTICLE 1 – (1) The objective of these Regulations is to set forth the procedures and principles regarding the achievement of scientific and ethical standards pertaining to topics such as the design, conduct, recording, reporting, validity and other aspects of clinical trials to be conducted on volunteer human subjects within the framework of European Union standards and Good Clinical Practice and to the protection of these volunteers within the scope of the said Regulation.

Scope

ARTICLE 2 – (1) These Regulations shall comprise clinical drug trials to be conducted on human subjects, non-drug clinical trials, trials conducted with medical devices, any type of clinical trials to be conducted by using a new surgical method, trial sites, real persons or legal entities to conduct these trials, bioavailability studies and bioequivalence studies as well as therapeutic trials.

(2) Observational studies, humanitarian programs for early access to drugs and non-drug standard therapeutic applications shall remain outside the scope of this Regulation.

Legal Basis

ARTICLE 3 – (1) This Regulation has been prepared on the basis of article 43 of the Decree Law Regarding the Organization and Duties of the Ministry of Health, dated 13/12/1983, with No. 181 and item (k) in clause one of Article 3 in the Fundamental Law Regarding Healthcare Services, dated 7/5/1987, with No. 3359;

(2) In parallel with the Directives 2001/20/EC and 2005/20/EC for the purpose of achieving harmonization with the EU legislation concerning drugs in the conduct of clinical drug trials.

Definitions

ARTICLE 4 – (1) For the purposes of these Regulations the following definitions shall apply;

a) Adverse effect: Any untoward effect arising with any administered dose of the investigational drug,

b) Adverse event: All untoward medical events with or without a causal relationship with the treatment administered,

c) Trial protocol: Document providing a detailed description of the objective, design of the clinical trial, the statistical methods to be applied and the arrangements relating to the trial,

d) Investigational product: Pharmaceutical form of the investigational product, placebo being tested or the reference product in the clinical trial,

d) Trial brochure: Documents relating to the clinical and non-clinical data on the investigational product(s),

e) Ministry: Ministry of Health,

f) Unexpected adverse effect: Adverse effect of the investigational product which is not included into the summary of product characteristics if it is registered or into the trial brochure if it is not registered,

g) Informed Consent Form: Written document indicating that the volunteer who will participate in the trial, or where necessary his/her legal representative, has decided to participate in the trial completely on his/her own free will upon receiving any relevant information on the trial as well as the importance of the administration and risks in terms of human health or, where the volunteer is not literate, the document indicating the verbal consent of the volunteer in the presence of at least one witness and bearing the signature of the witness,

ğ) Serious adverse event or effect: Any adverse event or effect that results in death, is life-threatening, requires hospitalization or leads to the prolongation of existing hospitalization, causes a persistent or significant disability or incapacity, congenital anomaly or defect,

h) Multi-center clinical trial: Clinical trial conducted according to a single protocol but at more than one site and therefore involving more than one investigator,

ı) Inspection: Activity conducted by the Ministry involving the inspection of the documents, records, quality assurance arrangements relating to the trial, the sites deemed as adequate by the Ministry for the conduct of clinical trials, centers belonging to the sponsor or contracted research organizations or other institutes, committees and institutions relating to the trial in terms of their compliance with this Regulation and other relevant legislations,

i) Sponsor: Individual, institute or organization that is responsible for the commencement, conduct or financing of a clinical trial; in case of absence of a sponsor of the trial, the trial coordinator in multi-center clinical trials and the responsible investigator in case of single trials,

j) Non-industrial advanced therapy medicinal product: Live cellular products and autologous tissues that may be administered in a hospital or under the responsibility of a specialized doctor, are prepared on the basis of a prescription or are custom-made for the patient, do not contain any industrial component in their manufacture, are used only within the relevant country and are prepared according to special standards,

k) Ethics Committee: Committees established upon Ministerial approval for the assessment of all clinical trials from an ethical viewpoint, for the purpose of providing a view from a scientific and ethical perspective with regard to the suitability of the trial protocol, investigators, adequacy of the trial sites, the methods and documents to be used in informing the volunteers, the consent to be obtained from these persons as well as other topics so as to ensure the protection of the rights, safety and well-being of the volunteers who will participate in the trial,

l) Volunteer: Ill or healthy individuals who participate in a clinical trial upon providing a written consent personally or via their legal representative in accordance with the provisions of this Regulation and other relevant legislations,

m) Observational study: Epidemiological studies on the approved drug indications, on patients whose treatment continues in line with updated diagnosis and treatment guidelines, where the data relating to the drug spontaneously prescribed are compiled,

n) Drug/drug for human use: Natural or synthetically derived active substance or combination of such substances administered to human subjects for the purpose of preventing, diagnosing and/or treating a disease, correcting, regulating or modifying a physiological function,

o) Non-drug standard treatment: The treatment, which is efficacy and safety has been demonstrated by at least one prospective randomized controlled study and which has been accepted upon being published on a journal included into the Science Citation Index or Science Citation Index Expanded,

ö) Clinical drug trial: Studies conducted on human subjects for the purpose of verifying or revealing clinical, pharmacological or other pharmacodynamic effects of one drug or multiple drugs, defining the adverse effects of the drug, designating its absorption, distribution, metabolism and excretion, investigating its efficacy and/or whether it is safe,

p) Advanced therapy medicinal product: Industrially manufactured stem/somatic cell therapy products and tissue engineering products,

r) Humanitarian Program for Early Access to Drugs: Program ensuring that the company developing the drug not

registered in Turkey and is or is not registered in other countries provides this drug free of charge to patients whose treatment with available medicinal products in Turkey has failed, who suffers from a seriously life-threatening disease and who does not have the chance to access the trials held in relation with this topic,

s) Good Clinical Practice: Rules encompassing topics such as the design, conduct, monitoring, budgeting, assessment and reporting of trials, protection of all the rights and bodily integrity of volunteers, preservation of the safety of trial data and to be complied with by all parties participating in the trial so as to ensure that the trials are conducted at international scientific and ethical standards,

ş) Clinical trial: Any type of trial such as clinical drug trials, non- drug clinical trials, trials conducted with medical devices and clinical trials conducted by using a new surgical method, conducted on human subjects in one or multiple centers,

t) Clinical Trials Advisory Board: Board established within the Pharmaceutical General Directorate upon Ministerial approval for the purpose of providing its opinion to the Ministry from a scientific and ethical viewpoint in topics relating to clinical trials,

u) Coordinator: In multiple center trials, the investigator responsible for ensuring the coordination between the responsible investigators of these centers, the Ethics Committee and the sponsor,

ü) Responsible Investigator: Physician or dentist who has completed his/her education on a branch of specialization relating to the topic of the trial and is responsible for the conduct of the trial,

v) Therapeutic trial: Treatment conducted by a specialized doctor in a hospital, in compliance with scientific rules, on patients that cannot be treated by known medical intervention methods defined within the scope of clause four of Article 90 in the Turkish Penal Code dated 26/9/2004, with No. 5237 or in cases where such treatment methods are highly risky, based on some concrete benefits obtained in relation with the treatment of the disease even if the scientific trial outcomes are not yet finalized, upon obtaining the consent of the patient or his/her legal representative,

y) Non Commercial Clinical Drug Trials: Trials conducted without the participation of the pharmaceutical industry in the assessment of the diagnosis, prevention and/or treatment of diseases, patient rehabilitation and the interventions performed with drugs used in long-term care and which do not bear a commercial purpose,

z) Orphan drug: All drugs used for rare diseases or conditions.

SECTION TWO

Protection of the Volunteers who will Participate in Clinical Trials,

Obtaining Consent for the Trial and Responsibility

General principles relating to the protection of volunteers

MADDE 5 – (1) The following requirements shall be fulfilled so as to able to conduct trials on volunteers:

a) The anticipated scientific benefits and public interest of the trial shall not be placed before the health of the volunteer who will participate in the trial and the potential risks to arise in terms of the health and other personality rights. In case it is agreed by the Ethics Committee that the benefits to be obtained are more than the potential risks to arise from the trial, the trial may be commenced with the permit of the Ethics Committee and the Ministry upon receiving an informed consent by observing personality rights. The trial may only be conducted of such conditions continue to be preserved.

b) No clinical trials shall be conducted on children, pregnant women, women in maternity period and nursing women and incapacitated persons. However, trials may be permitted upon obtaining the Ethics Committee and the Ministry permit, in children, pregnant women, women in maternity period, nursing women and cases of incapacitation if it is hoped that the trial may provide direct benefit for the volunteers and if the trial does not bear any predictable risk in terms of the health of the volunteers.

c) Volunteer rights and ethical rules shall be respected.

ç) The person volunteered to participate in the trial or his/her legal representative, shall be sufficiently informed in a comprehensible manner before the commencement of the trial by the responsible investigator or an authorized person from the trial team regarding the objective, methodology, expected benefits, predictable risks, difficulties, aspects which do not suit the health and personal characteristics of the person as well as the conditions under which the trial will be conducted and continued.

d) A consent indicating the volunteer will participate into the trial with his/her own free will shall be obtained and this will be documented with the Informed Volunteer Consent Form encompassing the aspects relating to the provision of information stipulated in item (ç). The Informed Volunteer Consent Form will be prepared in three copies; one of which shall be given to the volunteer upon being signed, one will be placed in the main trial dossier and one shall remain with the investigator.

e) The trial shall be designed in a manner so as to minimize pain, discomfort, fear and any risk related with the disease of the patient and his/her age. In the trials involving the participation of children, pregnant women, women in maternity period and incapacitated volunteers, the volunteers or their legal representatives shall be personally informed about the risks and phases of the progression related with the disease and this will be documented with the Informed Volunteer Consent Form.

f) At least one person from the investigation team shall be appointed for ensuring that the volunteer may obtain information when desired regarding his/her health and the course of the trial and to achieve contact so as to serve this purpose.

g) The volunteer may quit the trial with our without a justification upon his/her own accord and shall not incur any loss from his/her existing rights during the consequent medical follow-up and treatment due to quitting.

ğ) With the exception of the insurance coverage, the sponsor shall not propose any convincing incentive or monetary inducement in order to secure the participation or continued attendance of volunteers in the clinical trial. However, the expenses to arise from the participation of the volunteers in the trial shall be designated in the trial budget and covered from the said budget. In case of payment of a fee for the pharmacokinetic and bioequivalence studies, this shall be specified in the protocol.

h) Any trial that may disrupt the germ-line genetic identity of the volunteer shall not be conducted.

ı) Except for the permits granted by the Ministry required by the disease of the volunteers, volunteers shall not participate in more than one trial at once.

i) Decisions regarding the medical follow-up and treatment of the volunteers participating in the trial shall be adopted by the doctors or dentists bearing the professional qualities necessitated by these.

j) In case the information to be obtained from the trial is published, the identity of the volunteers shall not be disclosed.

Obtaining informed consent of volunteers in clinical trials

ARTICLE 6 – (1) Taking into consideration the points raised in Article 5, the following aspects shall be respected in obtaining the consent of volunteers who will participate in clinical trials:

a) In accordance with item (ç) in clause one of Article 5, subsequent to informing the volunteer with regard to the trial in a sufficient and comprehensible manner, he/she shall provide a written consent which will be documented with an Informed Volunteer Consent Form. In cases requiring a witness, those who are related with the trial can not act as witnesses.

b) In case genetic research will be conducted or germ cells such as sperm and ova in the sample obtained from the volunteer as part of the trials, a separate consent shall be obtained from the volunteer for each study.

c) In case of failure of the volunteer to give consent, his/her legal representative shall be authorized to do so.

ç) Consents shall not be obtained from the volunteer in an unlawful and unethical manner.

Participation of children in trials

ARTICLE 7 – (1) No trial shall be conducted on children. However, in cases directly related with the subject matter of the trial or in clinical conditions that may only be assessed in children or where the data obtained from trials conducted on adults need to be proven also in children, if the trial does not pose a predictable serious risk in terms of the health of the volunteer and it is hoped that the trial may provide a direct benefit for the volunteers, permit may be granted for the conduct of trials on children within the framework of below-mentioned points, provided that the aspects specified in Article 5 are taken into account.

a) In case the child has the capacity to make an evaluation of the information provided to him/her and reach an opinion regarding this topic, he/she shall be excluded from the trial in case he/she refuses to participate in the trial or makes a request for withdrawing from the trial at any phase.

b) A written consent of the legal representative shall be obtained upon being informed as per item (ç) in clause one of Article 5. The legal representative may take back the written consent whenever he/she desires, even if the trial does not lead to a negative impact on the health of the child.

c) The Ethics Committee shall be evaluated by a doctor specialized in pediatric health and diseases on clinical, ethical and psychosocial problems regarding the trial and the protocol shall be evaluated from this viewpoint.

ç) In the clinical trials to be conducted in children, no convincing incentive or financial inducement shall be offered besides for the mandatory expenses to arise with the participation of children in the trial.

Participation of pregnant women, women in maternity period and nursing women

ARTICLE 8 – (1) No trial shall be conducted on pregnant women, women in maternity period and nursing women. However, in case the subject matter of the trial is a clinical condition which is directly related with pregnant women, women in maternity period or nursing women, if the trial does not pose any predictable risk in terms of the health of the volunteers or it is hoped that it may provide a direct benefit on volunteers, permit may be granted for conducting trials on pregnant women, women in maternity period and nursing women within the framework of below-mentioned aspects upon taking into account the points stipulated in Article 5:

a) In case pregnant women, women in maternity period or nursing women refuse to participate in the trial or submit a request for withdrawing at any phase of the trial, they shall be excluded from the trial.

b) There should be a general medical opinion that there is no known risk of the investigational product on pregnant women, women in maternity period and nursing women or the benefits provided by the investigational product to pregnant women, women in maternity period or nursing women outweigh the risks to arise from this product.

Participation of incapacitated persons in the trial

ARTICLE 9 – (1) Trials shall not be conducted on patients in intensive care, rank and file and persons encompassed by the conditions of incapacity defined in Articles 405 - 408 of Turkish Civil Code No. 4721, dated 22/11/2001. However, in case the subject matter of the trial is directly related with incapacitated persons or which can be assessed only on incapacitated persons, or where the existing therapeutic options for the disease of the incapacitated person are fully consumed, permit may be granted for the conduct of trials on incapacitated persons within the framework of below-mentioned aspects provided that the points indicated in Article 5 are taken into account, if the trial does not bear any predictable risk in terms of the health of the incapacitated person and if it is hoped that the trial will provide a direct benefit for incapacitated persons:

a) The written consent of the legal representative shall be obtained upon providing information to the disabled person and/or his/her legal representative as per item (ç) in clause one of Article 5.

b) If the incapacitated person holds to capacity to reach an opinion upon evaluating the information provided to him/her, his/her request for refusing to participate in the trial or withdraw at any phase of the trial shall be taken into account and he/she will be excluded from the trial.

c) There should a general medical opinion that there is no known risk of the investigational product on incapacitated persons or the benefits to be provided by the investigational product to the incapacitated person outweigh the risks to arise from this product.

ç) No convincing incentive or financial proposal shall be offered for the clinical trials to be conducted on

incapacitated persons other than covering the mandatory expenses arising with the participation of incapacitated persons in the trial.

SECTION THREE

Ethics Committees

Structure of Ethics Committees

ARTICLE 10 – (1) Ethics committees shall be established by Ministerial approval in regions to be determined by the Ministry, in order to secure the rights, safety, and well-being of the volunteers to participate in the trials so as to deliver an ethical and scientific opinion on the trial protocol, suitability of investigators, adequacy of the sites where the trial will be conducted, methods and documents to be used in informing volunteers and the consent to be received from them and in other subjects concerning trials, to achieve volunteer safety and ensure that the trial conducted and monitored in accordance with the regulations, and to evaluate all clinical trials from an ethical viewpoint. Accordingly;

a) The Ministry shall determine the location and number of the regions where Ethics Committees will be established according to demand, and publish these on the Ministry's website. According to demand, the Ministry may permit more than one Ethics Committee to be established in one region, or can annul Ethics Committees where there is no more need for them.

b) Secretariat of the Ethics Committee may be established at the Health Directorate of the province where the Ethics Committee is located, or at a healthcare institute or organization to be approved by the Ministry.

c) In order to establish an Ethics Committee at selected regions, candidate list or lists for the Ethics Committee shall be prepared by the Provincial Health Directorate at the said province, university research hospitals, research and training hospitals and public hospitals or in accordance with the terms in clause three in case of personal applications; and these lists will be submitted to the Ministry. Following an evaluation, the Ministry shall choose the members of the Ethics Committee from these lists and approve the Ethics Committee.

ç) In case of no application from any one of the determined regions in order to establish an Ethics Committee, the Ethics Committee for the said region will be appointed by the Ministry.

d) Members of the Ethics Committee shall start their duty upon signing the security clearance document to be prepared by the Ministry and carry out their duties for two years. It is possible to be re-elected for membership.

e) Secretariat of the Ethics Committee will inform the Ministry of the applications to be made for Ethics Committee membership at least sixty days before the term of the Ethics Committee member expires. The Ministry shall approve one of these candidates. If the names of candidates are not submitted on time by the Ethics Committee secretariat, the new member in place of the one whose term is expired is appointed by the Ministry.

(2) The Ethics Committee shall consist of at least eleven, at most fifteen members. Ethics Committee will convene with the presence of two-thirds of its members and decide upon the simple majority of its members.

(3) Ethics Committees will consist of members with the following minimum qualifications;

a) At least three clinical physicians of various specialties, one being a pediatrician, who preferably participated in clinical trials conducted in accordance with Good Clinical Practice,

b) At least one pharmacologist, who has specialized in or obtained a Ph.D. in pharmacology, preferably an M.D.,

c) At least one biochemist, who has specialized in or obtained a Ph.D. in Biochemistry, preferably an M.D.,

ç) One medical ethics specialist or deontologist,

d) One pharmacologist,

e) An engineer working in the biomedical field, or in case no specialist is found, a lecturer in biophysics or

physiology who is a graduate of a school of medicine,

f) A biostatistician or if needed, a public health expert,

g) A member who is a law school graduate,

ğ) A member graduated from any university, who is not a healthcare professional, who does not work in a healthcare institute or organization and who does not have association with clinical trials,

(4) Where required, Ethics Committees may seek the opinion of experts of the relevant branch or a subsidiary branch and may invite these persons to the meeting as consultants.

(5) In order to abide by the principle of independence of Ethics Committees, at most five of the members of an Ethics Committee may be selected from the same institute.

(6) Rectors, Vice Rectors, Deans, Vice Deans, Provincial Directors of Health, and Head Physicians may not become members of the Ethics Committee.

(7) An Ethics Committee member may not undertake duties in more than one Ethics Committee simultaneously.

(8) Only one person from among mother, father, children or spouses may work in an Ethics Committee.

(9) Clinician, pharmacologist and biochemist members of the Ethics Committees shall be obliged to have received training and/or certificates at the courses/seminars whose content and conditions are determined by the Pharmaceutical General Directorate. The Ministry may stipulate that other members of the Ethics Committee and researchers to conduct clinical trials on volunteers to receive the said course/seminar training and/or certificate.

(10) Ethics Committee members shall comply with the confidentiality principle concerning all kinds of information they receive.

(11) An Ethics Committee member who has a connection with the trial's sponsor or who has a duty in the trial being investigated may not join the Ethics Committee discussions about the said trial.

(12) All kinds of clinical trials shall be evaluated by the Ethics Committee organized in accordance with this Article. A separate Ethics Committees will not be organized for clinical drug trials and non-drug clinical trials.

(13) The Ministry may inspect clinical trials with or without prior notice. Violations determined as a result of inspection shall be reported. The Ethics Committee has to undertake all corrections concerning these items within sixty days, in accordance with this Regulation and relevant legislation. Otherwise, the Ministry may annul the Ethics Committee and establish a new Ethics Committee.

(14) In subjects within the scope of this Regulation, an Ethics Committee or any other similar Ethics Committee may not be organized by other institutions.

Duties and powers of Ethics Committees

ARTICLE 11 – (1) The duties and powers of Ethics Committees shall be as follows:

a) The Ethics Committee shall deliver an opinion from scientific and ethical viewpoint on all kinds of clinical trials conducted on volunteers. Accordingly, it will deliver a scientific and ethical opinion on Phase I, Phase II, Phase III, and Phase IV drug trials, bioavailability and bioequivalence trials, and all other clinical trials such as those on non-drug products, genetic materials, medical devices and surgical methods. It shall be mandatory to comply with and implement these opinions.

b) The Ethics Committee shall announce its scientific and ethical opinion on clinical trials within forty-five days as of the date of application;

1) Its opinion on clinical drug trials to the Pharmaceutical General Directorate,

2) Its opinion on stem cell transplantation, tissue transplantation, genetic research and trials of a new medical

device to the General Directorate of Curative Services,

3) The Ethics Committee shall announce its opinion on studies other than those within the scope of sub-item (1) and (2) of item (b) of clause one only to the applicant and the approval of the Ethics Committee will be sufficient to start these trials.

c) In case the Ethics Committee requires additional information and explanations during the inspection process, the applicant shall be informed of all the necessary requests at once and the inspection process will be suspended until all required information and documents are submitted.

ç) While the Ethics Committee forms an opinion on the trial application, it shall evaluate:

1) The analysis of expected benefits and risks of the trial,

2) Whether the trial is based on a new hypothesis or not,

3) Whether the trial brochure is prepared regularly or not,

4) The written information submitted concerning the trial, the method used to obtain consent of volunteers, the validity of reasons for the trials to be conducted on incapacitated persons and children,

5) In case of injury or death including potential permanent health problems that may result from trials, the responsibility of the researcher or sponsor and the scope of the insurance certificate or policy drawn for volunteers (Phase IV studies shall be outside the scope of insurance),

6) In case there is any contract between the sponsor and the site where the trial is to be conducted concerning the awards and compensations approved for the researcher and volunteer, whether this contract is ethical or not,

7) Whether the sites where the trial is to be conducted meet the standards mentioned in Article 15 or not.

d) Non-commercial Clinical Drug Trials shall be evaluated in accordance with the relevant guideline.

e) When necessary, the Ethics Committee may observe the applications in the research phase and *in situ*.

f) In trials involving children, the Ethics Committee has to decide within the scope of the information mentioned in Article 7, clause one, item (c).

g) In case the Ethics Committee determines that this Regulation or other legislation is violated, that the requirements of the trial are no longer met, that the dependability or scientific validity of the trial has been forfeited or if it is informed of such, it shall notify the investigator, the sponsor and the Ministry.

ğ) For the Ethics Committees to function in a standard manner, the Ethics Committee Standard Operating Procedures shall be issued by the Ministry, published on the Ministry's website and updated when necessary.

h) Application Forms to be used shall be published on the Ministry's webpage and all clinical trial applications will be made in accordance with these forms. Applicants may not design or use any application forms other than these forms. Even if such an application is made, it shall not be accepted by the Ministry and the Ethics Committee.

ı) Ethics Committees shall submit a list of all their activities and the details of all their implementations to the General Directorate in annual reports. In these reports, they will define and discuss significant scientific and ethical problems encountered by the boards, inform about their backgrounds and give a list of the projects submitted to them.

i) Ethics Committees shall be obliged to immediately execute the directives of the Ministry.

SECTION FOUR

Clinical Trials Advisory Board

Composition of clinical trials advisory board

ARTICLE 12 – (1) The clinical trials advisory board shall be composed with Ministerial approval within the Pharmaceutical General Directorate. The Ministry will submit the information and documents relating to the application made in compliance with this Regulation to the Board for an opinion so as to form the basis of the permit to be granted by the Ministry.

(2) Clinical trials advisory board shall be composed of the following members, making a total of 20 members:

a) General Director of the Pharmaceutical General Directorate or the Deputy General Director to be assigned by him/her,

b) One member representing the General Directorate of Curative Services, at the minimum level of Department Chairman,

c) Two pharmacologists who have graduated from medical school and obtained their Ph.D. in the field of pharmacology or have completed their specialization; one pharmacologist who has graduated from the school of pharmacy, obtained his/her Ph.D. in the field of pharmacology or completed his/her specialization,

ç) One toxicologist,

d) Four clinical doctors who have participated as investigators in clinical trials organized in accordance with Good Clinical Practice, serving in medical faculties or training and research hospitals, with a professional experience of minimum five years, and who are specialized in different branches, one being pediatric health and diseases,

e) One medical ethics specialist or deontologist,

f) One biostatistician,

g) One medical genetic specialist,

ğ) One specialist working in the biomedical field,

h) One faculty member representing the Central Council of the Turkish Medical Association,

ı) One faculty member representing the Central Delegation of the Turkish Pharmacists' Association,

i) One faculty member representing the Central Delegation of the Turkish Dentists' Association,

j) One faculty member who is a legal expert and represents the Board of Directors of Turkish Bar Association,

k) One faculty member from the school of theology,

l) One member representing the Chairmanship of the Social Security Institute, minimum at the level of Department Chairman.

(3) The members indicated in items (a), (b) and (l) in clause two shall be designated by their institutes and appointed by the Minister. For the other members besides for these as well as each membership indicated in items (h), (ı), (i) and (j) one out of three names reported by relevant professional organizations shall be appointed by the Minister upon the proposal of the Pharmaceutical General Directorate.

(4) Clinical Trial Advisory Board shall convene under the chairmanship of the General Director of the Pharmaceutical General Directorate or the Deputy General Director to be appointed by him. Where necessary, a member to

be appointed by the General Director shall deputize to the Chairman.

(5) Board members shall start their duty upon signing the security clearance document to be prepared by the Ministry; and carry out their duties for two years. However, the Ministry may change the members of the Clinical Trials Advisory Board before the end of their term. It is possible to be re-elected form membership.

(6) Member(s) of the Clinical Trials Advisory Board who have a relation the sponsor of the trial or serve in the investigated trial shall not participate in the discussions of this trial.

(7) The members indicated in items (c), (ç) and (d) in clause two shall be obliged to receive training and certificate on the topic of Good Clinical Practice, the content and conditions of which will be designated by the Pharmaceutical General Directorate. The Ministry may stipulate that the members indicated in the other items receive training and certificate on Good Clinical Practice.

(8) Clinician members should have served as member of the Ethics Committee for a period of at least one year.

(9) Members indicated in items (c), (ç) and (d) in clause two shall not serve in another Ethics Committee during the term of their membership in the board.

Working procedures and principles of the clinical trials advisory board

ARTICLE 13 – (1) The working procedures and principles of the Clinical Trials Advisory Board shall be as follows:

a) Where deemed necessary by the General Directorate, it shall submit its opinion regarding the trials from an ethical viewpoint and fulfill the tasks assigned by the Ministry.

b) The Standard Operating Procedures to set the basis of the work of the Clinical Trials Advisory Board shall be designated by the Ministry and renewed, when necessary, upon informing the Ministry.

(2) The meetings of the Clinical Trials Advisory Board composed of twenty persons shall be conducted with the participation of at least twelve members, and decisions will be adopted with the vote of at least eleven members. The meeting dates of the Clinical Trials Advisory Board shall be designated by the Pharmaceutical General Directorate.

(3) Members who fail to participate in two consecutive meetings during his/her membership without any permission or an acceptable excuse shall be ended its membership by the Ministry.

(4) The member whose membership is ended due to any reason shall be replaced within two days by a new member bearing the same qualities, according to the procedure set forth in Article 12.

SECTION FIVE

Principles Relating to the Conduct of Trials

Phases of clinical drug trials

ARTICLE 14 – (1) The phases of the clinical drug trials shall be as follows:

a) Phase I: The clinical phase involving the experimentation for the determination of the pharmacokinetic characteristics, toxicity, bioavailability and the impact on bodily functions of the investigational product to be administered to a sufficient number of healthy volunteers selected according to the characteristics and nature of the trial or to ill volunteers as in oncology studies where it is not possible to conduct the study on healthy volunteers.

b) Phase II: The clinical trial phase involving the experimentation of the investigational product on a sufficient number of healthy volunteers selected according to the characteristics and nature of the trial, for the purpose investigating its therapeutic dose limits, clinical efficacy and safety.

c) Phase III: The clinical trial phase involving the experimentation of the investigational product on a sufficient

number of volunteer patients selected according to the characteristic and nature of the trial, in terms of its efficacy, safety, investigation of a new indication, different doses, new routes and methods of administration, new patient population and new pharmaceutical forms.

ç) Phase IV: The clinical trial phase conducted on a higher number of patients for further investigating approved indications of registered products, and the safety and efficacy of the suggested use of permitted products or making a comparison with other established therapies, products and methods.

Sites where clinical trials will be conducted and relevant standards

ARTICLE 15 – (1) Clinical trials may be conducted in hospitals that are suitable for ensuring the safety of volunteers and enable the conduct and follow-up of the trial in a sound manner and making of urgent interventions where necessary and avail of the staff, equipment and laboratory facilities that suit the nature of the trial.

(2) Bioavailability and bioequivalence studies may be conducted in medical institutes and institutions that avail of the facilities for conducing urgent interventions.

(3) Responsible investigator may include into the investigation team assisting investigators with suitable qualifications for the purpose of ensuring the fulfillment of relevant requirements and adoption of relevant measures for the safety of the patients; he/she shall indicate this on the application form.

(4) On the basis of Good Clinical Practice, the sites where clinical trials will be conducted shall ensure at least the following;

a) Relevant and adequate staff and equipment in line with the nature of the trial,

b) Relevant space and facilities for the storage and distribution in line with the nature of the investigational product,

c) Facilities and equipment that may enable the provision of suitable care service to the volunteers, including conditions that may require urgent intervention,

ç) Adequate facilities and equipment to enable the transfer of the volunteers to a more advanced medical institute, where necessary,

d) Adequate facilities and equipment to store the information and documents relating to the clinical trial and volunteers upon the completion of the trial, for the period envisaged in the Good Clinical Practice.

Permit application for centers where bioavailability and bioequivalence studies will be conducted

ARTICLE 16 – (1) Application shall be submitted to the Ministry with the information and documents indicated in relevant guidelines for obtaining permission for private or public centers to be established for the purpose of conducting bioavailability and bioequivalence studies.

(2) Within ninety days following the submission of the application, the Ministry shall grant permit for the study site upon verifying the accuracy of information and documents presented in inspections to be conducted by the Pharmaceutical General Directorate and designating that trial site fulfills the relevant requirement..

Application and permit for the trial

ARTICLE 17 – (1) The application dossier of the trial shall be prepared within the Good Clinical Practice Guidelines and other relevant guidelines, upon completing the application form on the webpage of the Ministry.

(2) The trial application shall be submitted by the sponsor to the Ethics Committee and the relevant General Directorate.

(3) Those who would like to conduct a trial within the scope of this Regulation shall apply to the Pharmaceutical General Directorate for any type of trial upon receiving the position opinion of the Ethics Committee, and to the General Directorate of Curative Services for stem cell transplantation, tissue transplantation, genetic trials and the experimentation

of new medical devices.

(4) The Ministry shall not grant permit for any trial not approved by the Ethics Committee. However, application shall be made directly to the Ministry for trials to be conducted diseases such as avian flu, severe acute respiratory syndrome (SARS) and Crimean Congo hemorrhagic fever whose treatment is not yet well known and for which it is essential to conduct clinical trials as well as trials on orphan drugs.

(5) The applicant may object to the decision of the Ethics Committee. In this case, the applicant shall apply to the Ministry with an objection petition. Where deemed suitable by the Ministry, the Clinical Trials Advisory Board shall assess the application from an ethical viewpoint and adopt its decision.

(6) If there are more than one Ethics Committees in the same region, the sponsor or the investigators may apply to the Ethics Committee of their choice.

(7) If there is no Ethics Committee in a settlement area, the sponsor or the investigators may apply to the Ethics Committee in another settlement area.

(8) In multi-center studies, the decision to be adopted by the Ethics Committee where the coordinator center is located and it will be not be necessary to have a separate Ethics Committee for each center. However, where deemed necessary, the Ministry may request for the adoption of a separate Ethics Committee decision for the other centers as well. The sponsor shall be obliged to a copy of the Ethics Committee approval received and the application dossier to the Ethics Committees in the settlement center where each trial center is located, for informative purposes.

(9) The Ethics Committee shall be obliged to make an evaluation within forty-five days as of the application date for the clinical trial submitted to them. Applications which are not evaluated within this period shall be evaluated by the Ministry upon the written application of the applicant and the dossier will be submitted to another Ethics Committee or the Clinical Trials Advisory Board. The relevant dossier shall be completed latest within sixty days as of the application date to the Ministry. The Ministry shall request for the justification from the relevant Ethics Committee that failed to evaluate the application in time, and will inspect the Ethics Committee where necessary. The Ministry shall take action in relation with the relevant Committee according to the justification provided and/or the inspection report.

Application to the Ministry and its timeframe

ARTICLE 18 – (1) The sponsor may apply simultaneously both to the Ethics Committee and the Ministry for any type of clinical trial before the commencement of the trial. Hence, the sponsor shall apply to the Pharmaceutical General Directorate for clinical drug trials and to the General Directorate of Curative Services for stem cell transportation, tissue transportation, genetic trials and studies for testing a new medical device.

(2) The correspondence to be made with the Ministry shall be conducted with the sponsor of the trial.

(3) In case of detection of any deficiency in the application dossier during the preliminary assessment by the relevant General Directorate, the need to complete the referred deficiency shall be reported to the sponsor. The evaluation process shall restart upon making up for the deficiency, in case the deficiency is not remedied in sixty days, it shall be regarded as rejected.

(4) In case the relevant General Directorate designates a case necessitating the knowledge of a specialist during the preliminary assessment, it send the dossier to the one its adequate commissions or to a Scientific Advisory Commission whose number of members and field of specialization will be designated by itself.

(5) The dossier undergoing the preliminary assessment shall be sent to the Clinical Trials Advisory Board in case this is deemed necessary by the relevant General Directorate.

(6) The applications shall be evaluated latest within sixty days.

(7) In the trials to be conducted with products bearing genetically modified organisms and trials to be conducted with products bearing somatic cell treatment or gene treatment an additional thirty-day period may be granted in addition to the sixty-day period. However, in case of need for receiving a specialist's outside the Ministry view or detailed assessments depending on the topic of the trial, an additional period of ninety days may be granted.

Commencement of clinical trials

ARTICLE 19 – (1) Even if the Ethics Committee grants approval for clinical drug trials, stem cell

transplantations, tissue transplantations, genetic trials and studies for testing a new medical device for clinical drug trials shall not be commenced without the permit of the General Directorate of Curative Services.

(2) The relevant General Directorate shall evaluate the scope of the insurance designating the adequacy of the measures that will compensate the losses to arise in the volunteers to participate in the trial are harmed or die and the budget relating to the costs to arise due to the participation of the volunteers in the study and the involvement of the investigators in the trial as well as the suitability of the rewarding.

(3) If the relevant General Directorate has taken a negative decision regarding the conduct of the trial, the relevant reasons shall be reported to the sponsor. The sponsor may conduct required amendments in the aspects indicated in the decision and may apply again once or object to the decision based on a justification. In case the amendments requested by the General Directorate are not fulfilled or in the failure of the presentation of an acceptable justification, the trial shall be rejected.

(4) In case it becomes necessary to conduct major amendments on the documents regarding the safety of volunteers during the conduct of the trial or due to the protocol, this protocol amendment shall be reported to the General Directorate so as to be approved by the sponsor. The General Directorate shall evaluate these amendments within thirty-five days and approve those which it deems adequate.

Conduct of the clinical trial

ARTICLE 20 – (1) Clinical trials shall be conducted as follows:

a) Clinical trials shall be conducted under the chairmanship of a responsible investigator who is a clinician medical doctor or a dentist, with a team that suits the nature of the trial. Responsible investigator should have completed its specialization or doctorate degree regarding the topic of the trial. Phase I clinical drug trials shall be conducted by a medical doctor pharmacologist on healthy volunteers. Phase I clinical drug studies related to oncology shall be conducted on patient volunteers by an oncologist and medical doctor pharmacologist.

b) Amendments to be made on the protocol after the commencement of the trial shall be reported to the General Directorate and the relevant Ethics Committee by the sponsor or the investigator. In case the Directorate fails to deliver its opinion regarding the protocol amendment within thirty-five days as of the application date, the protocol amendment shall be regarded as approved. However, it shall be necessary to obtain the approval of the relevant General Directorate for the protocol amendments indicated in clause four of Article 19.

c) Without prejudice to the aspects indicated in item (b) of this article, the sponsor or the investigator shall adopt urgent safety measures to protect the volunteers against the dangers that may arise in case of the emergence of a new condition that may affect the safety of the volunteers during the conduct of the trial or the development of the investigational product. The sponsor shall inform the relevant Ethics Committee as well as the relevant General Directorate about the new condition and the measures adopted. Otherwise, the Ministry may stop the trial.

ç) If the trial is not commenced on the date indicated in the application dossier despite being granted permit by the Ministry, the reasons for not commencing it shall be reported to the relevant Ethics Committee and the relevant General Directorate within fifteen days. If the trial is interrupted without being completed upon being commenced, the informative letter including the decision to discontinue it along with the relevant reasons and the measures adopted in relation with the maintenance therapy of the volunteers enrolled into the trial shall be added and submitted to the relevant Ethics Committee and the relevant General Directorate. The coordinator or the responsible investigator shall be obliged to report both to the relevant Ethics Committee and the relevant General Directorate that the trial has ended within ninety days as of the end of the trial.

d) The sponsor may transfer a part of its own duties to commercial or academic institutions working in compliance with scientific principles and Good Clinical Practices provided that a written contract is prepared and a permit is obtained from the Ministry. The transfer of the duties to a contracted research organization does not eliminate the potential legal and penal responsibility regarding transferred tasks of the sponsor. The sponsor and the contracted research organization shall be both responsible for the results of the jobs and transactions constituting the subject matter of the contract.

Suspension or prohibition of clinical trials

ARTICLE 21 – (1) If the Ministry determines that the requirements reported when granting a permit for the trial are not fulfilled or acts are made in violation of these requirements, it shall warn the sponsor or the investigator once by clearly indicating the measures to be adopted for remedying this situation and the timeframe during which they should be adopted; furthermore, it shall report this situation to the relevant Ethics Committee. In case of failure of the adoption of the

relevant measures within the designated timeframe, the Ministry shall suspend or prohibit the clinical trial.

(2) In case the information presented in the attachment of the application regarding the safety and scientific adequacy of the clinical trial as well as the working conditions are no longer valid, the Ministry may suspend or prohibit the clinical trial; moreover, it shall inform the sponsor and the relevant Ethics Committee about this situation. In cases where there is no evident risk for the volunteers, the views of the sponsor and/or investigator may be requested before the adoption of the decision to suspend or prohibit. In this case, the sponsor or investigators shall be obliged to submit to the Ministry their views regarding this topic within seven days.

(3) If the trial is conducted in a foreign country/countries, the decision to suspend or prohibit in relation with the clinical trial shall be reported to the competent authorities along with its justification where deemed necessary by the Ministry.

SECTION SIX

Investigational Products

Responsibility of the sponsor and responsible investigator regarding the investigational product

ARTICLE 22 – (1) The sponsor shall be responsible for the storage of the investigational product pursuant to its manufacture or import in conformity with the characteristics of the product, its distribution, delivery to the trial center, maintaining these conditions in the trial center, ensuring the return of unused products upon being collected from the trial center or their adequate disposal and keeping records throughout all this process or securing that these are preserved.

(2) The investigator in each center where the trial is conducted shall be responsible for taking delivery, preservation of investigational products, their distribution according to written requests, stock control, transactions to be conducted according to the protocol on the remaining part and keeping records.

(3) The responsible investigator shall appoint someone from the investigation team for these transactions. In case the quantity of the product used is high, also a pharmacist shall be appointed where necessary.

Manufacture, Importation and Labeling of Investigational Products

ARTICLE 23 – (1) It should be ensured that investigational products are manufactured in compliance with the rules specified in the Good Manufacturing Practices.

(2) Permit shall be obtained from the Ministry for the manufacture or import of the products to be used in the trials and only the sponsor can apply for this permit.

(3) The sponsor to conduct the manufacture or import of the investigational product shall fulfill the following requirements:

a) In the application to be submitted to the Ministry, it shall be documented that each batch of the investigational product to be manufactured or imported is manufactured and controlled in accordance with the product specifications indicated in the dossier at least under conditions that suit good manufacturing practice.

b) The samples pertaining to each batch of the products manufactured or imported for the purpose of conducting an investigation as well as the information and documents relating to them shall be preserved for a period of at least five years.

c) Medical devices shall be evaluated within the scope of the Regulation Regarding Medical Devices published on the Official Gazette dated 9/1/2007, with No. 26398 whereas active medical devices to be implanted in the body in accordance with the Regulation Regarding Active Medical Devices to be Implanted in the Body, published on said the Official Gazette.

ç) The label on the outer package and in the absence of an outer package, on the ready package on the outermost package shall be prepared in Turkish in conformity with the Good Manufacturing Practice Guidelines enforced within the scope of the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use published on the

Official Gazette dated 23/10/2003, with No. 25268.

Recall of investigational products

ARTICLE 24 – (1) In case the trial is interrupted, all of the products remaining with the investigator shall be forthwith recalled by the sponsor from the distribution sites and this shall be reported to the General Directorate within fifteen days along with the relevant documents, in the form of a report.

(2) Withdrawal of investigational products and the transactions and measures to be conducted in relation with withdrawn products shall be indicated to the relevant General Directorate in the report submitted.

SECTION SEVEN

Notification of Adverse Events and Serious Adverse Effects

Notification of adverse events

ARTICLE 25 – (1) Adverse events indicated in the protocol or the trial brochure or which emerge during the trial and need to be reported immediately, shall be reported to the relevant Ethics Committee and the relevant General Directorate during the timeframes indicated in the protocol.

(2) All serious adverse events shall be urgently reported to the relevant Ethics Committee and the relevant General Directorate whereas the detailed report will be submitted within eight days. A single code number shall be given to the volunteers participating in the study in the urgent report and the successive reports.

(3) Adverse events and/or laboratory findings defined as critical for safety assessments shall be forthwith reported to the sponsor within the period indicated in the protocol.

(4) In case of death of one of the volunteers participating in the trial, the investigator shall present to the sponsor, relevant Ethics Committee and the relevant General Directorate any type of additional information.

(5) The sponsor shall keep detailed records of all adverse events which are reported to him/her by the investigator(s). These records shall be submitted to the General Directorate upon request.

Notification of serious adverse effects

ARTICLE 26 – (1) The sponsor of the trial shall notify the relevant General Directorate and the relevant Ethics Committee about the serious, unexpected adverse effects during the clinical trial which resulted in death or are life-threatening, within maximum seven days as of the receipt of the referred information. Monitoring reports including the additional information regarding these cases within eight days as of the receipt of the information.

(2) All other serious unexpected adverse effects shall be reported by the sponsor to the Ministry and the concerned Ethics Committee within fifteen days pursuant to the first receipt of information. The sponsor shall also inform all investigators.

(3) The sponsor shall submit to the relevant General Directorate, once a year, the full list of observed serious suspected adverse effects, in a manner so as to encompass information relating to volunteer safety as well, along with the intermediary report form annexed to the Good Clinical Practice Guidelines, upon receiving the view of the relevant Ethics Committee. The General Directorate or the Ethics Committee may also request for a report in a shorter interval where deemed necessary or in case of short-term trials.

Other notifications

ARTICLE 27 – (1) In multi-center trials, the intermediary report and the final report shall be prepared taking as basis the forms included into the Good Clinical Practice Guidelines in a manner so as to encompass the results relating to all of the centers involved in the trial.

(2) The sponsor shall be responsible for informing the General Directorate about the notifications on a regular

basis.

SECTION EIGHT

Miscellaneous and Final Provisions

Training

ARTICLE 28 – (1) The Ministry may organize courses or seminars for the purpose of training qualified investigators and healthcare staff in the field of good clinical practice for ensuring standardization of the Ethics Committees. The Ministry shall approve and inspect the programs of seminars or courses to be organized by relevant organizations which they deem to be suitable.

Trial records and confidentiality

ARTICLE 29 – (1) All records relating to the clinical trial shall be duly preserved and kept for a period of at least ten years upon the completion of the trial. Basic documents shall be archived in a manner so as to be presented easily for the evaluation of the competent authority upon request.

(2) In case of transfer of the data and documents relating to the trial for any reason whatsoever; this shall be reported to the Ministry; the new owner shall be responsible for the preservation and archiving of the data or documents.

(3) Confidentiality of the documents relating to the trial is essential. These documents shall be presented only upon the request of legally authorized individuals or competent persons.

Inspection

ARTICLE 30 – (1) The Ministry shall inspect with or without prior notice the trials conducted in Turkey and abroad, the trial sites, the sponsor and the contracted research organization, the sites where the investigational products are manufactured, the laboratories where the analyses relating the trial are conducted, in terms on their compliance with the provisions of this Regulation and other relevant legislations. Depending on the result of the inspection, the trial shall be stopped if necessary by the Ministry.

(2) Good Clinical Practice inspectors shall be selected among medical doctors, pharmacists or clinical branch specialists suiting the characteristics of the study, with a sufficient training and experience regarding Good Clinical Practice. Good Clinical Practice inspectors shall be responsible for preserving the confidentiality of the information obtained during the inspection.

Responsibility

ARTICLE 31 – (1) Any legal and financial responsibility of the trial shall belong to the person, institute/organization, sponsor and contracted research organization conducting the trial.

(2) The examination and analysis fees of any investigational product used in the trial, as well as the devices and materials utilized in relation with the product shall be covered by the investigator or sponsor and will not be paid by the patient or social security institutes nor will they forced to pay these. However, the Ministry, Ministry of Finance and/or Chairmanship of the Social Security Institute may designate different procedures and principles for the drug, examination and analysis fees of the trials encompassed by non-commercial clinical drug trials.

(3) It shall be necessary for the real or legal persons that will conduct the trial to indicate in the application dossier the financing of the trial. However, if the trial is a project to be financed by local/foreign institutes or organizations such as universities, TÜBİTAK (Scientific and Technological Research Council of Turkey), DPT (State Planning Organization), if the financial situation of trial becomes in the acceptance of the trial project by organizations, it will be sufficient for the Ethics Committee to indicate this on the application form and there will be no need to indicate its financing in detail. Furthermore, when the project is accepted, the financing shall be sent with an additional letter in detail, and sent to the Ethics Committee and the Ministry by the person or institute responsible for correspondences before the commencement of the trial.

(4) The fact that an Informed Volunteer Consent Form from the volunteer participating in the trial shall not

eliminate the right of the volunteer to be compensated for any health damage incurred as a result of the trial.

Bans

ARTICLE 32 – (1) In case the trials encompassed by this Regulation are conducted in violation of the procedures and principles indicated in the Regulation and/or other relevant legislations, it shall be prohibited to publish the results of the trial. The names, surnames and titles of the real and legal persons as well as relevant institutes and organizations may be announced to the public via the media instruments deemed adequate by the Ministry.

(2) In case of violation of the provisions indicated in Article 20, relating to clinical trials, the trial may be suspended or banned by the Ministry. In case of elimination of the reasons for the prohibition or suspension, this shall be reported to the Ministry by the sponsor and the trial may be resumed in case it is deemed adequate by the Ministry.

Administrative sanctions and penalty sanctions

ARTICLE 33 – (1) The sponsor, responsible investigator(s) designated to have conducted trials in violation of the provisions of this Regulation may be banned to conduct trials for a temporary or permanent period of time by the Ministry.

(2) Turkish Penal Code with No. 5237 and the provisions of other legislations shall apply depending on the nature of the deeds, on those who act and conduct activities in violation of the provisions indicated in this Regulation.

Authority to make arrangements

ARTICLE 34 – (1) The Ministry shall be authorized to make any type of sub-arrangement for ensuring the enforcement of this Regulation.

Cases not encompassed by this Regulation

ARTICLE 35 – (1) In cases not encompassed by this Regulation, the provisions of the Convention for the Protection of the Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Law on the Ratification of the Convention on Human Rights and Biomedicine, published on the Official Gazette dated 9/12/2003, with No. 25311, Medical Deontology Regulations enforced with the Council of Ministers Decision dated 13/1/1960, with No. 4/12578, provisions of other relevant legislations and the provisions indicated in the Regulation Regarding Patients Rights published on the Official Gazette dated 1/8/1998, with No. 23420 regarding the rights of volunteers participating in the trial.

Revoked regulations

ARTICLE 36 – (1) Regulation Regarding Drug Trials published on the Official Gazette dated 29/1/1993, with No. 21480 and the Regulation Regarding Ethics Committee for Diagnosis and Treatment Protocols published on the Official Gazette dated 30/7/2000, with No. 24125.

Transition provisions

TEMPORARY ARTICLE 1 – (1) The Central Ethics Committee established as per Article 12 of the Regulation Regarding Clinical Trials published on the Official Gazette dated 29/1/1993, with No. 21480, shall dissolved within six months as of the enforcement date of this Regulation.

(2) Current Local Ethics Committees may accept new trial applications until 30/6/2009. Applications accepted by this date shall be finalized as per the provisions of the Regulation Regarding Clinical Trials, abolished with Article 36.

(3) The Local Ethics Committee shall hand over its tasks, responsibilities and trial dossiers to the Ethics Committee to be established in the closest location as per the provisions of this Regulation. If the Ethics Committee is not established, the trial dossiers will be preserved for a period to be designated by the Ministry. However, this period shall not exceed the date 31/12/2009 and the term of the Local Ethics Committees shall end.

(4) Applications submitted before the enforcement date of this Regulation for obtaining a permit shall be evaluated and finalized according to the provisions of the Regulation Regarding Clinical Drug Trials abolished with Article 36. However, for permitted and ongoing trials, the transactions relating to the withdrawal of the products remaining with the investigator in case of a change in the protocol, trial brochure, monitoring of adverse effects and events and informing that

the trial cannot be conducted.

Enforcement

ARTICLE 37 – (1) This Regulation shall become effective on 1/1/2009.

Execution

ARTICLE 38 – (1) The provisions of this Regulation shall be executed by the Minister of Health.