REGULATION

From the Ministry of Health:

REGULATION ON CLINICAL TRIALS

CHAPTER ONE
Purpose, Scope, Basis and Definitions

Purpose

ARTICLE 1 – (1) This Regulation aims to regulate the procedures and principles to provide scientific and ethical standards for the design, conduct, record-keeping, reporting, validity of and for the other matters relating to clinical trials to be conducted on human volunteers and protection of volunteers' rights in accordance with the international agreements and conventions to which Turkey is a party and standards of the European Union and good clinical practice.

Scope

ARTICLE 2 – (1) This Regulation covers drug clinical trials to be performed on humans with drugs or preparations, even if they are registered or permitted, observational drug clinical trials, observational medical device clinical trials; clinical trials with any other substances or products which may be studied on humans, including medical devices, advanced therapy medicinal products, traditional herbal medicinal products, cosmetic raw materials or products; bioavailability and bioequivalence (BA/BE) studies; comparability studies for biosimilar products; trials with industrial or non-industrial advanced medicinal products; stem cell transplantation trials on humans, organ and tissue transplantation trials, surgical trials, and gene therapy trials; as well as clinical trial facilities and natural or juristic persons who will conduct these trials.

(2) Non-interventional clinical trials are not covered by this Regulation, except observational drug studies and observational medical device studies.

Basis

ARTICLE 3 – (1) This Regulation is issued:

a) based on Article 43, Decree Law #181 of 13/12/1983 on the Organization and Functions of the Ministry of Health, and supplemental article 10, Fundamental Law on Health Services #3359 of 07/05/1987; and

b) in parallel with Directives 2001/20/EC and 2005/28/EC on Good Clinical Practice, of the legislation of the European Union concerning medicinal products and

c) in parallel with Directives 93/42/EEC and 90/385/EEC of the European Union on Medical Devices and Active Implantable Medical Devices.

Definitions

ARTICLE 4 – (1) For the purposes of this Regulation,

a) 'Adverse effect' means any untoward effect occurred in a subject upon administration of any dose of the investigational product or upon use of the investigational medical device;

b) 'Adverse event' means any untoward medical occurrence in a volunteer, whether or not having a causal relationship with the treatment administered;

c) 'Investigator's brochure' means the documents relating to the clinical and non-clinical data on the investigational product(s)/medical device(s);

ç) 'Trial protocol/plan' means a document that details the objective, design, methodology, statistical methods to be used and trial-related arrangements;

d) ‘Investigational product’ means the pharmaceutical form of the substance being investigated, the placebo being tested or the reference product used in the clinical trial, or the medical device for clinical trial use;
e) ‘Ministry’ means the Ministry of Health;
f) ‘Unexpected adverse effect’ means an adverse effect of the investigational product, which is not included in the summary of product characteristics if it is a registered product, or in the investigator’s brochure if it is not an authorized product, or not specified in the user manual of an investigational medical device;
g) ‘Informed Consent Form’ means a written document, signed and dated by the parties, showing that the volunteer has agreed to participating in trial entirely by his or her free will, or, if the volunteer or his/her legal representative is illiterate or the volunteer is visually impaired, a written document signed by a witness unaffiliated with the study, showing that the volunteer has consented orally in the presence of at least one witness, after the volunteer who is to be enrolled in the study, or his/ her legal representative when necessary, has been fully informed on the trial, procedures and given information on the significance of risk to human health;
ğ) ‘Serious adverse event or effect’ means any adverse event or effect that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability or incapacity, or causes a congenital anomaly or defect;
h) ‘Multi-center clinical trial’ means a clinical trial conducted at more than one site according to a single protocol, and is, therefore, involving more than one principal investigators;
ı) ‘Inspection’ means activities of the Ministry of inspecting study-related documents and records and locations where they are archived, the quality assurance arrangements and sites that have been approved by the Ministry for conducting a clinical trial, the centers owned by sponsors or contract research organizations, or other organizations, boards or institutions related to the study, including ethics committees, for compliance with this Regulation or other applicable regulations;
i) ‘Sponsor’ means an individual, institution or organization responsible for the initiation, conduct and/or funding of a clinical trial; or the direct principal investigator for trials to be conducted in collaboration with the Ministry of Development, The Scientific and Technological Research Council of Turkey (TÜBİTAK) or scientific research projects of universities; or, where there is no institution or organization sponsoring the trial, the coordinator of the study for multi-center trials; or the principal investigator for individual trials;
j) ‘Industrial advanced medicinal product’ means an advanced therapy medicinal product which is derived from human/animal cells or tissues, prepared from a single source for use in multiple humans, or which, even if prepared for use by a single person, contains an unapproved industrial product/gene therapy product;
k) ‘Non-industrial advanced medicinal product’ means live cellular products and autologous tissues prepared according to special quality standards for use solely in the country concerned, which may be administered at a hospital under specialist supervision, is dispensed on prescription or upon a patient-specific order, and contains no industrial constituents for which manufacturing does not include approval for such use;
l) ‘Ethics committee’ means an independent board, constituted and approved by the Ministry based on fields of clinical research to provide scientific and ethical opinion on matters related to the trial protocol, the eligibility of the investigators, the adequacy of facilities wherein the study will be conducted, and the methodology and documents to be used for informing volunteers, as well as the consent obtained from these individuals and other aspects relevant to research, with a view to protecting the rights,

safety and well-being of study volunteers; in order to ensure and follow up that the study is conducted in compliance with the legislation;
m) 'Traditional herbal medicinal product' means any preparations whose medicinal herbal ingredients are bibliographically proved to have been in use prior to the application date for at least fifteen years in Turkey or in a member state of the European Union , for a period of at least thirty years in other countries, which, by virtue of their composition and purpose, are designed and intended for use without the supervision of a physician for diagnostic purposes or for prescription or monitoring of treatment, and which have specific indications appropriate to traditional herbal medicinal products, and which are exclusively for administration in accordance with the a specified dose and posology, for oral, external or inhalation route of use;
n) 'Gene therapy clinical trial' means studies aimed to treat disease in humans by eliminating deficiency of genes whose genetic code is known and functional investigations have been completed;
o) 'Non-interventional clinical trial' means any trial not involving direct intervention in the patient by a physician, including all observational studies, survey studies, retrospective archive screening such as file and image records, investigations with biochemical, microbiological, pathological and radiological collection materials such as blood, urine, tissue or radiological images or other materials obtained during routine examination, testing, analytical or therapeutic procedures, studies with cells or tissue cultures, investigations for identification with genetic materials not having the nature of a gene therapy clinical trial, studies performed within confines of the nursing care, dietary studies with food additives, studies on body physiology such as exercise, studies conducted based on anthropometric measurements, or studies evaluating life habits;
ö) 'Volunteer' means a healthy or unhealthy individual who is to participate in a clinical trial upon the written consent of the individual, personally, or that of the individual's legal representative, according to this Regulation and other applicable legislation;
p) 'Observational drug study' means epidemiological studies to collect data on a spontaneously prescribed drug, in patients undergoing treatment in the indications for which the product has been registered in Turkey according to the current diagnostic and therapeutic guidelines of the Ministry and epidemiological studies described on the Guideline of the Observational Studies on Drugs;
r) 'Observational medical device study' means epidemiological studies to collect data on a medical device bearing the CE marking, spontaneously used for intended use as described in medical device user manual;
s) 'Drug' or 'medicinal product for human use' means any natural, synthetically or biotechnologically derived active substance or combination of substances administered to humans with a view to prevent, diagnose and/or treat a disease, or to correct, regulate or modify a physiological function;
ş) 'Drug clinical trial' means any investigation in human conducted at one or more sites, in order to verify or reveal clinical, pharmacological or other pharmacodynamic effects, investigate the efficacy and/or safety of one or more drug, identify the adverse effects of the drug; or to determine absorption, distribution, metabolism and excretion of the drug(s);
t) 'Advanced therapy medicinal product' means gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products, or combined advanced therapy medicinal products manufactured industrially or subjected to industrial processes;
u) 'Human oriented compassionate use program' means a program for a medicinal product not registered in Turkey – whether or not approved in other countries – which

is provided without charge by the originator/supplier company in accordance with the procedures and principles described in the Guideline on Compassionate Use Program to a group of patients with a life-threatening disease or a condition that is severely disruptive of the quality of life, who cannot be enrolled in relevant clinical trials in the subject matter and in whom treatment using medicinal products which are registered/permitted by the Ministry of Health or standard therapeutic methods have failed or it is no longer possible to use these treatments;

ü) 'Good clinical practice' means the rules that must be followed by the parties involved in a clinical trial, covering a set of regulations for designing, conducting, monitoring, budgeting, evaluating and reporting clinical trials to provide assurance that trials are conducted according to the international scientific and ethical standards; for protecting the rights and physical integrity of volunteers; ensuring reliability of study data and protecting confidentiality;

v) 'Vulnerable' means any person who meets the criteria of disability as described in Article 405 and 408 of the Turkish Civil Code #4721 of 22/11/2001, including patients under intensive care and privates and corporals conscripted for military service;

y) 'Clinical trial' means any scientific research in human volunteers or in materials collected from them;

z) 'Advisory Board for Clinical Trials' means a board that will be established at the Ministry within the General Directorate of Pharmaceuticals and Pharmacy to provide opinion to the Ministry on matters related to clinical trials;

aa) 'Coordinator' means an investigator holding a doctorate or medical residency degree who serves a coordinating function in a multi-center trial between the principal investigators of the individual sites and the Ministry, the ethics committee and the sponsor;

bb) 'Cosmetic product' means any preparations or substances which have been prepared to be applied to various external parts of the human body, e.g., epidermis, nails, hair system, lips and external genital organs, or to teeth and oral mucosa with a view to achieving the sole or essential purpose of cleaning them, perfuming them, changing their appearance and/or correcting body odors and/or protecting them or keeping them in good condition;

cc) 'Principal investigator' means, with respect to interventional studies, a physician or dentist holding a doctorate or medical residency degree in the branch relating to the trial scope who is responsible for the conduct of the study; and with respect to non-interventional studies, means the person holding a doctorate or medical residency degree who is responsible for the conduct of the study;

çç) 'Contract Research Organization (CRO)' means an independent organization operating according to good clinical practice principles to whom the sponsor has delegated all or some of its duties and authorizations in connection with the clinical trial by a written contract;

dd) 'Medical device' means any instrument, apparatus, appliance, software, accessory or other materials, manufactured by its manufacturer specifically for diagnostic and/or therapeutic use, whether used alone or in combination, including software to perform its intended function, which is intended by its manufacturer for use in humans for the purpose of:

1) Diagnosis, prevention, monitoring, treatment or alleviation of disease,

2) Diagnosis, monitoring, treatment, alleviation or relief of an injury or disability,

3) Investigation, modification or replacement of an anatomical or physiological process,

4) Contraception,

and which does not achieve its principal intended action in the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

ee) 'Medical device clinical trial' means systematic research or studies conducted on volunteers at one or more sites for the purpose of evaluating the safety and/or performance of a medical device.

CHAPTER TWO
Protecting of, Providing Insurance for and Obtaining Consent for the Trial from Study Volunteers, and Responsibility

General principles for protecting volunteers, and providing insurance

ARTICLE 5 – (1) In addition to obtaining the permission of the Ministry of Health, the following requirements apply for using any therapeutic procedures or tools, or medicinal products or preparations – whether registered or permitted – or traditional herbal medicinal products or medical devices in humans for purposes of scientific research:

a) The benefits for science and the society expected from a trial can not prevail over the health of the volunteers involved in the trial, or over any potential risks to their health or the other personal rights. It is essential that the study does not have any foreseeable noxious and permanent effects on human health. Where, with respect to Phase I, Phase II, Phase III and Phase IV drug clinical trials, medical device clinical trials, bioavailability and bioequivalence studies, comparability studies for biosimilar products, clinical trials with advanced therapy medicinal products, observational drug studies, observational medical device studies, clinical trials with industrial advanced medicinal products and non-industrial advanced medicinal products, gene therapy clinical trials, stem cell transplantation trials, organ and tissue transplantation trials or investigations of novel surgical procedures, it is concluded by the Ethics Committee concerned that the expected benefits of a trial overweigh the potential risks, with due regard for their personal rights and that the consent of the volunteers is obtained in line with the applicable procedure, the trial may be initiated after relevant ethics committee approval and the Ministry's approval. The trial may only be continued for as long as these conditions are continuously met.

b) No clinical trial may be conducted in children, pregnant women, postpartum or breastfeeding women and vulnerable individuals. However, in cases where the volunteers are expected to directly benefit from the trial and the trial carries no serious foreseeable risk to the well-being of the study volunteers, permission may be granted to a trial in children or vulnerable individuals or during pregnancy, lactation or the postnatal period, with the approval of the ethics committee and permission of the Ministry, provided that the volunteers' informed consent form has been obtained according to the applicable procedure.

c) Prior to participation in the trial, the volunteer, or the volunteer's legal representative, will be informed by an investigator from the trial team, sufficiently and in a manner comprehensible to the volunteer or the volunteer's legal representative, on the objective, methodology, expected benefits, foreseeable risks, challenges, and any aspects unfavorable to the volunteer's health or personal characteristics, as well as the conditions under which the study will be conducted and carried out, and that the volunteer is free to withdraw from the trial whenever the volunteer so wishes.

ç) The volunteer's consent will be obtained that he or she will be participating in the trial by his or her free will, and this will be documented on a Informed Consent Form including the information described in paragraph (c) above. The Informed Consent Form will be issued in two copies. One copy will be delivered to the volunteer against signature, and the other copy will be retained by the investigator.

d) It is essential that the trial does not involve any procedures that inflict pain on the volunteer to a degree that would be incompatible with human dignity. The trial shall be designed in a manner to minimize pain, discomfort, fear, and any risks related to the patient's condition or age. In trials involving children, pregnant, postpartum or breastfeeding women, specific warning on the risks and the stages of progression associated with the disease will be provided to these individuals or their legal representatives, and this will be documented on the Informed Consent Form.

e) At least one person from the trial team will be appointed for the volunteer to contact and get information at any time on his or her health or on the progress of the study.

f) Volunteers may withdraw from the trial at their own discretion, with or without giving a reason, at any time of they wish to, and may not be deprived of any of their rights during subsequent medical follow up and treatment.

g) The sponsor may offer no compelling incentive and/or financial benefit, except insurance coverage, to encourage patients to participate or remain in the study. However, expenses associated with volunteers' participation in the trial and any reduction in the personal income of healthy volunteers resulting from workday loss will be specified in the trial budget and will be reimbursed from the trial budget.

ğ) No trials may be conducted that involves disrupting the genetic structure of a volunteer's germ cells.

h) A volunteer may not simultaneously participate in more than one clinical trial; however, where a volunteer's condition necessitates, the Ministry may give permission to the volunteer to participate in more than one trial.

ı) Decisions related to the medical follow-up and treatment of a study volunteer will be given by a physician or dentist possessing the professional qualifications necessary for taking such decisions.

i) Volunteer's identification details will not be disclosed when publishing the results from a clinical trial.

(2) In order to secure the volunteers against harm(s) from the clinical trial, insurance must be provided to volunteers who take part in clinical trials that fall within the scope of this Regulation. Some clinical trials, however, are exempted from the insurance requirement since they carry no or an acceptable level of risk to study volunteers. Clinical trials that are subject to insurance requirement and clinical trials that are excluded from this requirement are as follows:

a) All observational studies are excluded from the insurance requirement.

b) Insurance must be provided to volunteers participating in Phase I, Phase II and Phase III drug clinical trials, BA/BE studies, and comparability studies for biosimilar products. However, Phase IV drug clinical trials are exempted from the insurance requirement.

c) Clinical trials with traditional herbal medicinal products are exempted from the insurance requirement, provided that the trial is conducted using the traditional use of these products. Otherwise, insurance is mandatory.

ç) Clinical trials with medical devices bearing the CE marking conducted in line with the intended purpose of such devices as described in the medical device user manual are exempted from the insurance requirement; however, in all other clinical trials with medical device, it is mandatory to provide insurance for the study volunteers.

d) Non-interventional clinical trials are exempted from the insurance requirement.

e) Procedures which can be performed routinely at health institutions or organizations for collecting blood, urine, saliva or similar materials are exempted from the insurance requirement.

f) Aspects related to providing insurance for volunteers in connection with examination, diagnostic, testing or therapeutic procedures, as well as surgical procedures, other than the ones specified in this subclause, which may be applied to

study volunteers during a clinical trial will be regulated by a guideline that will be issued on the subject matter by the General Directorate of Health Services.

Obtaining the volunteer's consent in clinical trials

ARTICLE 6 – (1) Having regard to the considerations highlighted above in Article 5, the following guidelines must be followed when obtaining the consent of volunteers who will participate in a clinical trial:

a) After the volunteers are given information sufficiently and in a manner comprehensible to them on the clinical trial according to Article 5, Paragraph (c), their written consent will be obtained and documented on the Informed Consent Form. In cases when a witness is necessary, persons affiliated with the trial may not act as a witness.

b) In the event that the study involves conducting genetic and/or pharmacogenetic investigation of samples collected from volunteers, or collecting germ cells such as sperms or ovules, the separate volunteer's consent must be obtained for each study.

c) In cases where the volunteer is unable to consent, his/her legal representative is competent.

ç) Samples or similar data obtained from individuals, including during non-interventional studies, can not be used without permission of the individual or that of his/her legal representative.

d) Signed consent of the owners or of their legal representatives must be obtained for each of using collected blood, urine, tissue, radiological images or similar materials for purposes of clinical research. However, in the event that it is no longer possible to contact a material's owner or his or her legal representative, the collection will be regarded anonymous, provided that the ethics committee establishes that this is the case and gives its permission. The data collected from a collection may be used for purposes of clinical research, provided that the owner's identification details are kept confidential. The anonymization procedure described in this subparagraph applies to materials collected prior to issuance of this Regulation, and will not apply to materials collected after this Regulation enters into force.

Participation of children in a clinical trial

ARTICLE 7 – (1) Clinical trial can not be done on children. However, where the volunteer of the clinical trial is directly related to children or is a clinical condition that can be investigated only in children, or it is necessary to verify the applicability of adult data to children, it may be permitted to conduct a clinical trial on children within the below premise, taking account of the considerations highlighted above in Article 5, provided that the clinical trial carries no foreseeable serious risk to volunteers' well-being and it is expected that the clinical trial will directly benefit the volunteers:

a) If the child is capable to assess the information provided to him or her and reach a conclusion on the matter, all information relevant to the clinical trial will be communicated to the child in an appropriate manner. If the child refuses to participate in the clinical trial or requests to withdraw from the clinical trial at any phase, he or she will be removed from the clinical trial.

b) The ethics committee may not approve a clinical trial in children unless a favorable view for conducting the clinical trial in children has been given by a pediatric psychiatrist or a pediatrician, or, in the case of a clinical trial in children related to pediatric dentistry, by a dentist who holds a doctorate or medical residency degree in pediatric dentistry.

c) A common medical view must exist that the investigational product carries no known risk to children.

ç) The written consent of the legal representative will be obtained after he/she is informed in the manner described in Article 5, Paragraph (c). The legal representatives may withdraw their written consent at their discretion, even if the clinical trial causes no unfavorable effect on the children.

d) The ethics committee concerned will be informed on the clinical, ethical, psychological and social issues associated with the clinical trial, by a pediatric psychiatrist or a pediatrician, or, in the case of a clinical trial in children related to pediatric dentistry, by a dentist who holds a doctorate or medical residency degree in pediatric dentistry, and give consideration to the protocol accordingly.

e) No compelling incentive and/or financial benefit may be offered in connection with a clinical trial in children, other than the covering of necessary expenses arising from children's participation in the clinical trial.

Participation of pregnant, postpartum or breastfeeding women in a clinical trial

ARTICLE 8 – (1) Clinical trial can not be done on pregnant, postpartum or breastfeeding women. However, where the volunteer of the clinical trial is directly related to pregnant, postpartum or breastfeeding women or is a clinical condition that can be investigated only in pregnant, postpartum or breastfeeding women, it may be permitted to conduct a clinical trial in pregnant, postpartum or breastfeeding women within the below premise, taking account of the considerations highlighted above in Article 5, provided that the clinical trial carries no foreseeable serious risk to volunteer and fetal/infant health and it is expected that the clinical trial will directly benefit the volunteers:

a) If they refuse to participate in the clinical trial or request to withdraw from the clinical trial at any phase, pregnant, postpartum or breastfeeding women will be removed from the clinical trial.

b) The written consent of pregnant, postpartum or breastfeeding women will be obtained after informing them in the manner described in Article 5, Paragraph (c).

c) The ethics committee may not approve the clinical trial without a favorable opinion – with respect to fetal/infant health – for conducting the clinical trial in pregnant women has been given by a perinatologist or a gynecologist/obstetrician, or in the case of a clinical trial in postpartum or breastfeeding women, by a neonatologist or a pediatrician.

ç) A common medical view must exist that the investigational product carries no known risk to pregnant, postpartum or breastfeeding women or to the fetus/infant.

d) No compelling incentive and/or financial benefit may be offered in connection with a clinical trial in pregnant, postpartum or breastfeeding women, other than the covering of necessary expenses arising from their participation in the clinical trial.

Participation of vulnerable individuals in a clinical trial

ARTICLE 9 – (1) Clinical trials can not be done on vulnerable individuals. However, where the subject of clinical trial is directly related to the vulnerable or is a clinical condition that can be investigated only in the vulnerable and all therapeutic options available to treat the vulnerable individual's condition have been exhausted, it may be permitted to conduct a clinical trial in the vulnerable within the below premise, taking account of the considerations highlighted above in Article 5, provided that the clinical trial carries no foreseeable serious risk to health and it is expected that the clinical trial will directly benefit the vulnerable:

a) The written consent of the legal representative will be obtained after informing the vulnerable or his or her legal representative in the manner described in Article 5, Paragraph (c).

b) If a vulnerable individual is capable to assess the information provided to him or her and reach a conclusion on the matter, he or she will be immediately removed from

the clinical trial if the person refuses to participate in the clinical trial or requests to withdraw from the clinical trial at any phase.
c) A common medical view must exist that the investigational product carries no known risk to the vulnerable.
ç) The ethics committee concerned will be informed on the clinical, ethical, psychological and social issues associated with the clinical trial by a psychiatrist and a physician specialized in a field relevant to the subject of study, and give consideration to the protocol accordingly.
d) No compelling incentive and/or financial benefit may be offered in connection with a clinical trial in the vulnerable, other than the covering of necessary expenses arising from their participation in the clinical trial.

CHAPTER THREE
Structure, Operating Procedures and Principles, and Duties of Ethics Committees
Organization of Ethics Committees

ARTICLE 10 – (1) Ethics committees, comprised of not less than seven and not more than fifteen members with at least one of them a non-health care professional and one a jurist, and the majority consisting of health care professionals holding a doctorate or medical residency degree – will be assembled in order to perform a scientific and ethical assessment of the trial protocol, the design and suitability of the trial, the inclusion and exclusion criteria, the suitability of investigators, the adequacy of the clinical trial sites, and the methods and documents used to inform the volunteers and the consents obtained from the individuals, as well as any other aspects pertinent to the clinical trial, with a view to ensuring that the volunteers' rights, safety and well-being is protected and the study is conducted and monitored according to the regulations.
(2) While ethics committee members can hold a seat on only one of the ethics committees mentioned below in Paragraph 4 of this article, persons holding a doctorate, medical residency or master's degree in the field of medical ethics (deontology) may serve on more than one of those committees.
(3) Not less than three of the ethics committee members must be from outside the institution which provides secretarial services to the ethics committee.
(4) Ethics committees will be assembled as an Ethics Committee for Drug Clinical Trials, an Ethics Committee for Bioavailability/Bioequivalence Trials, or an Ethics Committee for Non-drug Clinical Trials, depending on the field of clinical research. However, at centers where clinical trials are conducted infrequently, it is possible to assemble only an Ethics Committee for Clinical Trials to review all clinical trials, excluding bioavailability/bioequivalence trials and comparability studies for biosimilar products.
(5) In places where an ethics committee is unavailable, the applications will be made to the ethics committee concerned in the nearest locality.
(6) An Ethics Committee for Bioavailability/Bioequivalence Trials will be assembled in provinces where these types of studies are conducted, to approve bioavailability/bioequivalence trials and/or comparability studies for biosimilar products after reviewing them for ethical and scientific aspects. Where multiple centers for Bioavailability/Bioequivalence exist in a city, a single Ethics Committee for Bioavailability/Bioequivalence Trials will be established therein to review the applications of all of those centers. However, where necessary, the Ministry may increase the number of Ethics Committees for Bioavailability/Bioequivalence Trials in the same city.
(7) Ethics committees will be established with Ministry approval within universities upon the proposal of the rector, within Refik Saydam Hıfzısıhha Center upon the proposal of the President of Refik Saydam Hıfzısıhha Center, or at training and research hospitals upon the

proposal of the chief physician, and commence functioning as of the approval date by the Ministry.

(8) The ethics committees will correspond directly with the Ministry, through their respective secretariats.

(9) Ethics committees who fail to operate in line with the ethical guidelines, or fail to meet the requirements laid down in the Ethics Committee Standard Operating Procedure, or found in a Ministry audit to be lacking the space, secretarial services, archiving services or equipment essential to fulfilling the function of an ethics committee will be issued a warning by the Ministry. The approval mentioned above in Paragraph (7) may be withdrawn if the ethics committee fails to address the issues that gave rise to the warning within the prescribed timeframe.

(10) An Ethics Committee for Drug Clinical Trials will consist of members that have at least the following qualifications:

a) Specialist physicians, at least one of whom with experience as an investigator in a clinical trial that was organized according to the guidelines for good clinical practice;

b) A pharmacist or doctor of medicine holding a doctorate or medical residency degree in pharmacology;

c) A biostatistician or physician holding a doctorate or medical residency degree in public health;

ç) A person holding a doctorate, medical residency or master's degree in medical ethics (deontology), if available;

d) A jurist;

e) A non-health care professional.

(11) An Ethics Committee for Bioavailability/Bioequivalence Trials will consist of members that have at least the following qualifications:

a) Specialist physicians, at least one of whom with experience as an investigator in a clinical trial that was organized according to the guidelines for good clinical practice;

b) A pharmacist or doctor of medicine holding a doctorate or medical residency degree in pharmacology;

c) A biostatistician or physician holding a doctorate or medical residency degree in public health;

ç) A pharmacist holding a doctorate degree in pharmaceutical technology;

d) A pharmacist or chemist holding a doctorate degree in pharmaceutical chemistry or analytical chemistry;

e) A person holding a doctorate, medical residency or master's degree in medical ethics (deontology), if available;

f) A jurist;

g) A non-health care professional.

(12) An Ethics Committee for Non-drug Clinical Trials will consist of members that have at least the following qualifications:

a) Persons holding a doctorate or medical residency degree, at least one of whom with experience as an investigator in a clinical trial that was organized according to the guidelines for good clinical practice;

b) A biostatistician or physician holding a doctorate or medical residency degree in public health;

c) An engineer or expert in the field of biomedicine, or, if unavailable, a biophysicist or physiologist who is preferably a medical graduate;

ç) A person holding a doctorate, medical residency or master's degree in medical ethics (deontology), if available;

d) A jurist;

e) A non-health care professional.

(13) An Ethics Committee for Clinical Trials will consist of members that have at least the following qualifications:

a) Persons holding a doctorate or medical residency degree, at least one of whom with experience as an investigator in a clinical trial that was organized according to the guidelines for good clinical practice;

b) A pharmacist or doctor of medicine holding a doctorate or medical residency degree in pharmacology;

c) A biostatistician or physician holding a doctorate or medical residency degree in public health;

ç) An engineer or expert in the field of biomedicine, or, if unavailable, a biophysicist or physiologist who is a preferably medical graduate;

d) A person holding a doctorate, medical residency or master's degree in medical ethics (deontology), if available;

e) A jurist;

f) A non-health care professional.

Operating procedures and principles of ethics committees

ARTICLE 11 – (1) Operating procedures and principles of ethics committees are the following:

a) All clinical trials falling within the scope of this Regulation will be reviewed by relevant ethics committees established according to Article 10 above.

b) Ethics committees are independent in their function of reviewing and approving clinical trial applications from a scientific and ethical perspective. The decisions of an ethics committee shall not be approved separately by the President of Refik Saydam Hıfzısıhha Center, the rector, the dean, or the chief physician.

c) Sponsors making an application to an ethics committee have recourse to raising a complaint or objection against a committee decision. Such complaints and objections will be raised with the General Directorate of Pharmaceuticals and Pharmacy, and reviewed by the Advisory Board for Clinical Trials.

ç) No ethics committee or a separate board or other organ may be established within other institutions or organizations to perform the function of an ethics committee for purposes of reviewing matters falling within the scope of this Regulation. However, institutions or organizations concerned may establish an ethics committee with the designation of "Ethics Committee for Non-Interventional Clinical Trials" and set its membership structure and roles, and operating procedures and principles to review matters that fall outside the scope of this Regulation.

d) Ethics committee members are obligated to comply with the confidentiality requirement for all information that has been made available to them. Members will take office upon signing a confidentiality agreement and a letter of commitment which will be drawn up by the Ministry.

e) Ethics committee member(s) who are affiliated with the study sponsor or have a role in the study being reviewed may not take part in ethics committee discussions and nor in the voting on the study concerned, nor may they have their signature under the committee decision.

f) Ethics committee members will convene with the two thirds majority of total number of members, and adopt decisions by the favorable vote of a simple majority of its full membership.

g) Ethics committee members' office term is two years. Any members who fail to attend three consecutive or five non-consecutive meetings without being excused throughout membership will be automatically removed from membership. Members whose terms expire may be reappointed. If a member whose term has expired or removed from membership is a non-healthcare professional or jurist member, a

member possessing the same qualifications will be reappointed in his or her place. In the event that any other member is removed from membership, a member holding a doctorate or medical residency degree will be appointed in his or her place.

ğ) Where necessary, ethics committees may solicit the written opinion of experts in a relevant field or subsidiary branch, and invite them to attend meetings as an advisor.

h) Ethics committees will resolve according to article 7 on trials which involve children.

ı) Ethics committees will resolve according to article 7 on trials which involve pregnant, postpartum or breastfeeding women.

i) Ethics committees will resolve according to article 9 on trials which involve vulnerable individuals.

j) For ethics committees in order to function in a standardized manner, the Ministry will establish an Ethics Committee Standard Operating Procedure and release on the Ministry website, updating it as necessary. Ethics committees carry out their functions within the frameworks of these standards.

Duties of ethics committees

ARTICLE 12 – (1) An ethics committee may monitor a clinical trial approved by it, with or without prior notice. Moreover, the Ministry may ask an ethics committee to monitor a clinical trial. The ethics committee submits its monitoring report to the relevant general directorate at the latest within ten days. The reports will be evaluated by the general directorate concerned.

(2) The Ethics Committee for Drug Clinical Trials has the following duties:

a) Gives its scientific and ethical opinion on Phase I, Phase II, Phase III and Phase IV clinical trials in volunteer with any investigational product other than a medical device, clinical trials with advanced therapy medicinal products, observational studies with drugs, clinical trials with traditional herbal medicinal products and efficacy and safety studies with cosmetic products or raw materials.

b) Ethics committees will compose their opinion and communicate it to the applicant within thirty days after the application date.

c) Permission of the Ministry is required to commence a clinical trial that has been approved by ethics committee. The study sponsor will make an application to the General Directorate of Pharmaceuticals and Pharmacy to obtain permission of the Ministry.

ç) Should additional information or clarifications become necessary during the ethics committee review, all of the requests will be communicated to the applicant in a single request. A second request will not be made to the applicant. The review process will be withheld until the required data and documents are submitted to the ethics committee.

d) When composing its opinion on the trial application, the ethics committee will take account of:

1) an analysis of the anticipated benefits, harm and risks from the trial,

2) whether the trial is based on scientific data and a new hypothesis,

3) in the case of first-in-human studies, the necessity of first performing the study in a non-human in vitro environment or in a sufficient number of animals,

4) whether scientific data obtained in a non-human in vitro environment or from experiments in animals have, as far as the study objectives are concerned, reached sufficient maturity to warrant conducting the study in humans also,

5) an evaluation of the contents of the investigator’s brochure and whether it has been prepared in due form,

6) the documented information submitted relating to the study, the method used for obtaining the consent of volunteers, and the justification for conducting the study in pregnant, postpartum or breastfeeding women, or children or the vulnerable who are incapable of consenting,

7) the responsibility of the investigator or the sponsor in the event of injury or death, including permanent health problems potentially resulting from the study, and the coverage of the insurance policy or certificate for both them and study volunteers,

8) the suitability of the entire trial team having a role in the study,

9) whether the agreement, if any, executed between the sponsor and the institution where the trial will be conducted concerning the compensatory arrangements deemed acceptable for the investigator and volunteers is ethical,

10) whether the reduction of income of healthy volunteers taking part in a Phase I drug clinical trial, resulting from workday losses, is provided and covered in the trial budget,

11) whether the institutions where the trial will be conducted meet the standards set forth in article 16 herein,

12)The observational studies with drugs are evaluated in accordance with the relevant guidelines.

(3) The Ethics Committee for Bioavailability/Bioequivalence Trials has the following duties:

a) Gives its scientific and ethical opinion on bioavailability and bioequivalence studies in volunteers, as well as comparability studies for biosimilar products.

b) Ethics committees will compose their opinion and communicate it to the applicant within fifteen days after the application date.

c) Permission of the Ministry is required to commence a clinical trial for which scientific and ethical approvals have been obtained. The sponsor will make an application to the General Directorate of Pharmaceuticals and Pharmacy to obtain permission of the Ministry.

ç) Should additional information or clarifications become necessary during the ethics committee review, all of the requests will be communicated to the applicant in a single request. A second request will not be made to the applicant. The review process will be withheld until the required data and documents are submitted to the ethics committee.

d) When composing its opinion on the trial application, the ethics committee will take account of:

1) an analysis of the anticipated benefits, harm and risks from the trial,

2) the documented information submitted, relating to the study and the adequacy of the method used for obtaining the consent of volunteers,

3) the responsibility of the investigator or the sponsor in the event of injury or death, including permanent health problems potentially resulting from the study, and the coverage of the insurance policy or certificate of study volunteers,

4) the suitability of the entire trial team having a role in the study,

5) whether the agreement, if any, executed between the sponsor and the institution where the trial will be conducted concerning the compensatory arrangements deemed acceptable for the investigator and volunteers is ethical,

6) whether the institutions where the trial will be conducted meet the standards set forth in article 16 herein,

7) whether the costs associated with volunteers' participation in the trial and the reduction of volunteers' income resulting from workday losses are provided and covered in the trial budget.

(4) The Ethics Committee for Non-drug Clinical Trials has the following duties:

a) Gives its scientific and ethical opinion on all non-drug clinical trials to be conducted in human beings at one or more sites, including clinical trials with medical devices, observational studies with medical devices, trials with industrial advanced medicinal products or non-industrial advanced medicinal products, gene therapy clinical trials, stem cell transplantation studies, organ and tissue transplantation studies and surgical studies in human volunteers. However, in cases where the objective of a trial mentioned in the preceding sentence is working on a medicinal product used for research, then the study will be deemed a drug clinical trial and reviewed by the Ethics Committee for Drug Clinical Trials.

b) Ethics committees will compose their opinion and communicate it to the applicant within thirty days after the application date.

c) Clinical trials with medical devices, observational studies with medical devices, trials with industrial advanced medicinal products or non-industrial advanced medicinal products, gene therapy clinical trials, investigations of novel surgical procedures, stem cell transplantation studies, and organ and tissue transplantation studies and surgical studies that have been given scientific and ethical approval must obtain the permission of the Ministry before commencing. For applications for studies other than the ones mentioned in this paragraph, the approval of the ethics committee is sufficient and the permission of the Ministry is not required. For observational studies with medical devices and clinical trials with medical devices, the sponsor should make an application to the General Directorate of Pharmaceuticals and Pharmacy, and for other trials, to the General Directorate of Health Services, in order to obtain permission of the Ministry.

ç) Should additional information or clarifications become necessary during the ethics committee review, all of the requests will be communicated to the applicant in a single request. A second request will not be made to the applicant. The review process will be withheld until the required data and documents are submitted to the ethics committee.

d) When composing its opinion on the trial application, the ethics committee will take account of;

1) an analysis of the anticipated benefits, harm and risks from the trial,

2) whether the trial is based on scientific data and a new hypothesis,

3) whether scientific data obtained in a non-human in vitro environment or from experiments in animals have, as far as the study objectives are concerned, reached sufficient maturity to warrant conducting the study in humans also,

4) an evaluation of the contents of the investigator’s brochure and whether it meets the requirements,

5) the documented information submitted relating to the study, the method used for obtaining the consent of volunteers, and the justification for conducting the study in pregnant, postpartum or breastfeeding women, or children or the vulnerable who are incapable of consenting,

6) the responsibility of the investigator or the sponsor in the event of injury or death, including permanent health problems potentially resulting from the study, and the coverage of the insurance policy or certificate of study volunteers,

7) the suitability of the entire trial team having a role in the study,

8) whether the agreement, if any, executed between the sponsor and the institution where the trial will be conducted concerning the compensatory arrangements deemed acceptable for the investigator and volunteers is ethical,

9) whether the institutions where the trial will be conducted meet the standards set forth in article 16 herein.

(5) The Ethics Committee for Clinical Trials has the following duties:

a) Gives its scientific and ethical opinion on safety and efficacy studies with cosmetic products and raw materials, and on all types of clinical trials in volunteers, excluding Bioavailability/Bioequivalence studies and comparability studies for biosimilar products.

b) Ethics committees will compose their opinion and communicate it to the applicant within thirty days after the application date.

c) Permission of the Ministry is required to commence Phase I, Phase II, Phase III or Phase IV drug clinical trials, clinical trials with advanced therapy medicinal products, observational studies with drugs, observational studies with medical devices, clinical trials with traditional herbal medicinal products, clinical trials with medical devices and safety and efficacy studies of cosmetic products or raw materials that have been given scientific and ethical approval by the ethics committee. The sponsor makes an application to the General Directorate of Pharmaceuticals and Pharmacy to obtain permission of the Ministry.

ç) Permission of the Ministry is required to commence studies with industrial advanced medicinal products and non-industrial advanced medicinal products, gene therapy clinical trials, studies with a novel surgical procedure, stem cell transplantation studies, and organ or tissue transplantation studies that have been given scientific and ethical approval by the ethics committee. The sponsor makes an application to the General Directorate of Health Services to obtain permission of the Ministry.

d) For clinical trials other than those mentioned in subparagraphs (c) and (ç), the approval of the ethics committee is sufficient and it is not necessary to additionally obtain permission from the Ministry.

e) Should additional information or clarifications become necessary during the ethics committee review, all of the requests will be communicated to the applicant in a single request. A second request will not be made to the applicant. The review process will be withheld until the required data and documents are submitted to the ethics committee.

f) When composing its opinion on the trial application, the ethics committee will take account of;

1) an analysis of the anticipated benefits, harm and risks from the trial,

2) whether the trial is based on scientific data and a new hypothesis,

3) the necessity of first performing the study in a non-human in vitro environment or in a sufficient number of animals,

4) whether scientific data obtained in a non-human in vitro environment or from experiments in animals have, as far as the study objectives are concerned, reached sufficient maturity to warrant conducting the study in humans also,

5) an evaluation of the contents of the investigator's brochure and whether it meets the requirements,

6) the documented information submitted relating to the study, the method used for obtaining the consent of volunteers, and the justification for conducting the study in pregnant, postpartum or breastfeeding women, or children or the vulnerable who are incapable of consenting,

7) the responsibility of the investigator or the sponsor in the event of injury or death, including permanent health problems potentially resulting from the study, and the coverage of the insurance policy or certificate of study volunteers,

8) the suitability of the entire trial team having a role in the study,

9) whether the agreement, if any, executed between the sponsor and the institution where the trial will be conducted concerning the compensatory arrangements deemed acceptable for the investigator and volunteers is ethical,
10) whether the reduction of income of healthy volunteers taking part in a Phase I drug clinical trial, resulting from workday losses, is provided and covered in the trial budget,
11) whether the institutions where the trial will be conducted meet the standards set forth in article 16 herein,
12) The observational studies with drugs are evaluated in accordance with the relevant guidelines.

CHAPTER FOUR
Organization, Duties, and Operating Procedures and Principles of the Advisory Board for Clinical Trials

Organization of the Advisory Board for Clinical Trials

ARTICLE 13 – (1) An Advisory Board for Clinical Trials will be established within the General Directorate of Pharmaceuticals and Pharmacy of the Ministry, with the Minister's approval.

(2)The Advisory Board for Clinical Trials will comprise of members specified in supplemental article 10 of Health Services Fundamental Law numbered 3359 and dated 07/05/1987.

Duties and operating procedures and principles of the Advisory Board for Clinical Trials

ARTICLE 14 – (1) The Advisory Board for Clinical Trials has the following duties:

a) Reviews complaints filed against ethics committees and objections raised against ethics committee decisions, and gives its opinion to the Ministry.

b) Upon the request of the Ministry, gives its opinion on matters related to clinical trials requiring an expert opinion which have been referred to the Ministry by ethics committees or by parties to a clinical trial.

(2) Operating procedures and principles of the Advisory Board for Clinical Trials are the following:

a) At its first meeting, the Board selects a deputy chairman among its members.

b) The Advisory Board for Clinical Trials convenes upon the request of the chairman or deputy chairman.

c) Members appointed to the board serve for term of two years, and may be reappointed at the end of their term.

ç) Any member who fails to attend three consecutive or five non-consecutive meetings without being excused will be automatically removed from membership. A member possessing the same qualifications as the removed member will be appointed in his or her place.

d) The Advisory Board for Clinical Trials meets with the two thirds majority of total number of members, and adopt decisions with the favorable vote of a simple majority of its full membership.

e) Should it be necessary, the Board may consult the view of experts and invite them to the Board for hearing their view.

f) The Standard Operating Procedures to provide basis for the activities of the Advisory Board for Clinical Trials will be set by the Ministry, and updated where necessary.

g) The secretarial services for the board will be provided by the General Directorate of Pharmaceuticals and Pharmacy.

CHAPTER FIVE
Principles for Conducting Trials

Phases of drug clinical trials

ARTICLE 15 – (1) Drug clinical trials have the following phases:

a) Phase I: Represents the stage of clinical research wherein an investigational product is investigated by administering it to a sufficient number of healthy volunteers, or to unhealthy volunteers when it is impossible to work with healthy volunteers, who have been selected according to the nature and character of the study, to evaluate its pharmacokinetics, toxicity, and effects on physiological functions.

b) Phase II: Represents the stage of clinical research wherein an investigational product is investigated by administering it to a sufficient number of patient volunteers who have been selected according to the nature and character of the study to evaluate its therapeutic dose limits, clinical efficacy and safety.

c) Phase III: Represents the stage of clinical research wherein an investigational product is investigated by administering it to a sufficient number of patient volunteers who have been selected according to the nature and character of the study to evaluate its efficacy, safety, new indications, different doses, new routes and modes of administration, a new patient population or new pharmaceutical forms.

ç) Phase IV: Represents the stage of clinical research in a large number patients where products registered in Turkey are further investigated in terms of their approved indications, or in the case of products permitted in Turkey, for their safety and efficacy characteristics against their recommended use, or for purposes of comparing them with other established treatments, products or procedures.

Clinical trial sites, standards, and applications for authorization

ARTICLE 16 – (1) Clinical trials may only be conducted at centers for health practice and research established within universities, including Gülhane Military Medical Academy (GATA), approved centers for research and development subordinate to universities, Refik Saydam Hıfzıssıhha Center and the Ministry's teaching and research hospitals which are suitable for and possess appropriate staff, equipment and laboratory means that enable ensuring the safety of research subjects and proper conduct and monitoring of a clinical trial, and appropriate emergency care should it be necessary.

(2) When necessary, clinical trials conducted at centers mentioned above may be supplemented with other health institutions or organizations meeting the criteria specified herein, provided it will be under coordination and responsibility of these centers.

(3) Phase I drug trials, BA/BE trials and comparability studies for biosimilar products:

a) These studies will be conducted at health institutions or organizations subordinate to the Ministry or universities or at centers for research and development approved by the Ministry which possess the necessary means to provide emergency care.

b) Centers established for conducting these studies may not commence operating without obtaining approval of the Ministry. Applications to obtain Ministry approval will be made to the General Directorate of Pharmaceuticals and Pharmacy, using the application form posted on the Ministry's website and relevant annexes, in accordance with applicable guidelines. The Ministry will give its approval for the trial site within ninety days after the application, provided that during the inspection of proposed trial sites by the General Directorate of Pharmaceuticals and Pharmacy the accuracy of the data and documents submitted with the application is demonstrated, and the trial site is shown to meet the necessary requirements. The Ministry will conduct subsequent

inspections of these sites every three years, or in shorter intervals as may be deemed necessary, and may either renew its previous approval or suspend the site's operations depending on the inspection outcome.

c) Centers that obtain approval from the Ministry for the trial site may commence the activities described in this paragraph, to the extent that such centers will be obligated to obtain the approval of relevant ethics committee and permission of the Ministry for each study that they will conduct.

(4) Sites where clinical trials will be conducted on the basis of the Guideline for Good Clinical Practice must minimally have:

a) the necessary staff and equipment at an adequate level, appropriate to the nature of the study,

b) the facilities and means necessary for storing and dispensing the investigational product in a manner appropriate to its nature,

c) the means and equipment to provide appropriate care to volunteers, including cases requiring emergency care,

ç)the sufficient means and equipment to enable transferring volunteers to a more advanced health institution/organization, where necessary, and

d) the sufficient means and equipment to retain the data and documents relating to the clinical trial and volunteers, for the period prescribed in the Guideline for Good Clinical Practice, after the study is completed.

Clinical trial application and authorization

ARTICLE 17 – (1) The application dossier for a clinical trial will be prepared according to the Guideline for Good Clinical Practice and other applicable guidelines, using the application form and its relevant annexes posted on the Ministry's website, and will be reviewed for Ministry permission and ethics committee approval according to this Regulation and the guidelines to be issued by the Ministry.

(2) In multi-center clinical trials, the scientific and ethical approval will be obtained of the ethics committee in the locality where the coordinating center is located. Notifications will be made to ethics committees in places where the other sites are located.

(3) The application for a clinical trial will be made to the relevant ethics committee or general directorate by the sponsor, consisting of natural/juristic person(s), or by a contract research organization domiciled in Turkey appointed by the sponsor. If the sponsor has no representative domiciled in Turkey, the application for a clinical trial must be submitted through a contract research organization domiciled in Turkey.

(4) Applications to obtain Ministry approval for conducting a clinical trial that have been granted ethical and scientific approval with any substances or products which and which may involve investigation in human beings, including clinical trials with medical devices, BA/BE trials, comparability studies for biosimilar products, Phase I, Phase II, Phase III and Phase IV drug clinical trials, clinical trials with advanced therapy medicinal products, observational studies with drugs, observational studies with medical devices, clinical trials with traditional herbal medicinal products and cosmetic products or raw materials, will be made to the General Directorate of Pharmaceuticals and Pharmacy.

a) For clinical trials with Class III medical devices or with implants or long-term invasive devices in Class IIa or Class IIb, the study sponsor or a contract research organization delegated by the sponsor will, upon the approval of the ethics committee concerned, make an application to the General Directorate of Pharmaceuticals and Pharmacy, and the application will be evaluated within sixty days after the notification date.

b) For all clinical trials with medical devices, excluding the ones mentioned in subparagraph (a), and all other drug clinical trials will be evaluated within not more than thirty days by the relevant general directorate.

(5) Applications to obtain Ministry approval for conducting clinical trials with industrial advanced medicinal products or non-industrial advanced medicinal products, gene therapy clinical trials, stem cell transplantation trials, organ or tissue transplantation trials and clinical trials with a novel surgical procedure which have been given scientific and ethical approval will be made to the General Directorate of Health Services. These applications will be evaluated within not more than sixty days.
(6) If the general directorate concerned adopts an unfavorable decision regarding the request for conducting the clinical trial, this decision will be notified to the applicant, together with the rationale for the decision. The sponsor will be granted a single opportunity to resubmit the application after making amendments to address the issues raised in the decision, or to file a reasoned objection against the decision. If the requested changes are not fulfilled or an acceptable justification cannot be offered, the general directorate concerned may reject the clinical trial.
(7) In the case of clinical trials with cellular therapies using products containing genetically modified organisms or products involving gene therapy, the thirty days specified for Ministry approval may be extended for an additional thirty days. However, in cases where it becomes necessary to hold detailed deliberations or to consult non-Ministerial third party experts, the timeline may be extended further by an additional ninety days, depending on the subject matter of the study.

Commencement of clinical trials
ARTICLE 18 – (1) Clinical trials that have been granted scientific and ethical approval by the ethics committee but require the permission of the Ministry may not be commenced without the permission of the relevant general directorate.
(2) If, after the commencement of a clinical trial, the need arises to make any of the amendments described in the Guideline for Good Clinical Practice, such amendment(s) will be notified to the relevant ethics committee and than to the general directorate for the approval by the sponsor. Should the amendments be found acceptable, the ethics committee will approve them within fifteen days, and the general directorate concerned within thirty days, to the extent they find the amendments acceptable.

Conduct of clinical trials
ARTICLE 19 – (1) A clinical trial will be conducted in the following manner:

a) Clinical trials falling within the scope of this Regulation will be conducted by a team suitable for the nature of the study, led by a principal investigator. Principal investigator must hold a doctorate or medical residency degree in the branch of study, or in an auxiliary branch. Phase I drug clinical trials, BA/BE studies and comparability studies for biosimilar products will be conducted by a suitable team and at least one pharmacologist who is a doctor of medicine.

b) Reserving the provisions made in Article 18, Paragraph 2, the sponsor and/or the investigator will taken any urgent safety precautions necessary to protect the volunteers against hazards that may arise in the event of new circumstances emerging during the conduct of a clinical trial or in connection with development of the investigational product, which may impact on volunteers' safety. The principal investigator and/or the sponsor will notify the relevant ethics committee or general directorate on these new circumstances and the precautions taken. Otherwise, the Ministry will suspend the study.

c) If a clinical trial, although permitted by the Ministry, cannot be commenced on the date specified in the application dossier, the reasons underlying such delay will be notified within fifteen days to the relevant general directorate. This timeframe may be, should it be necessary, extended by the general directorate concerned. If a trial, after it has been commenced, is stopped prematurely, an informational notice containing the

decision to stop the trial, together with the underlying reasons, and a description of the measures for maintaining the treatment of volunteers who have been enrolled in the study, will be submitted to the relevant general directorate. The sponsor or the coordinator will report the end of trial to the relevant general directorate within ninety days after the study ends.

ç) In order to ensure the conditions and precautions necessary for the safety of patients, the principal investigator may recruit sub-investigators from other institutions possessing the necessary qualifications to its team, and specify it on the application form.

d) The sponsor may delegate some of its duties to a contract research organization operating according to scientific guidelines and good clinical practice, provided that a written contract is executed and information is given to the Ministry. Delegation of duties to a contract research organization will not annul the sponsor's potential civil and penal liability in connection with such delegated duties. The sponsor and the contract research organization have joint responsibility for the contracted activities and their outcome.

Suspension or termination of a clinical trial

ARTICLE 20 – (1) The Ministry will immediately suspend a clinical trial when or if it is detected that any of the conditions that were met at the time of authorization are no longer met during the course of trial. If these conditions are not met, or it is concluded that they cannot be met within the prescribed timeframe, or if the volunteers' safety will be compromised in the mean time, the clinical trial will be directly suspended.

(2) In cases not involving an obvious risk to volunteers, the sponsor and/or investigator may be requested to submit their view on the issue. In that case, the sponsor or investigators will submit their opinion to the Ministry within seven days.

(3) If a clinical trial is also being conducted in third countries, the decision to suspend or terminate the clinical trial and the underlying reasons will be reported to such countries' competent authorities, if so deemed necessary by the Ministry.

CHAPTER SIX
Investigational Products

Responsibility of the sponsor and principal investigator in connection with the investigational product

ARTICLE 21 – (1) The responsibility rests with the sponsor to ensure that the investigational product, after it has been manufactured or imported, is stored, dispensed and delivered to the trial site in a manner compliant with the product's characteristics, that these conditions are maintained at the trial site, that unused products are recovered from the trial site or are properly destroyed, and that a record of all of these processes is maintained or caused to be maintained.

(2) The responsibility rests with the principal investigator at each center for accepting the delivery of products, maintaining them, dispensing them according to written instructions and/or the study protocol, checking the inventory, and following the protocol requirements for any remaining products and keeping the records.

(3) The principal investigator will appoint a pharmacist from the trial team to perform these processes.

Manufacture, importation, and labeling of investigational products

ARTICLE 22 – (1) It must be assured that the investigational product, if it is a medical device, has been manufactured according to the standards issued by the European Union, or if it is a tissue or cell, according to the Regulation on the Safety and Quality of Human Cells and Tissue and Related Centers, published in the Official Gazette numbered #27742 and dated 27/10/2010. For all other investigational products, an assurance must be given that the product has been manufactured according to the prescriptions of the Guideline for Good Manufacturing Practice.
(2) Permission of the Ministry shall be obtained for manufacture and importation of investigational products; for medical devices, permission is necessary only for importation. The application to obtain such permission may be submitted by either the sponsor or a contract research organization authorized by the sponsor.
(3) Sponsors who will manufacture or import an investigational product must meet the following requirements:

a) The application made to the Ministry must include documentation that each batch of the investigational product to be manufactured or imported was manufactured and controlled at least according to the standards of good manufacturing practice, and in line with the product specifications as indicated in the dossier.

b) Samples from each batch of the investigational product manufactured or imported, and its relevant data and documents, must be retained for not less than five years.

c) The investigational product will be labeled in Turkish on the outer packaging, or if it has no outer packaging, on the outermost packaging, in accordance with the Guideline for Good Manufacturing Practice which entered into force according to the Regulation on Manufacturing Plants of Medicinal Products for Human Use, published in the Official Gazette numbered #25268 and dated 23/10/2003.

Withdrawal of investigational products
ARTICLE 23 – (1) In the event of suspension of a clinical trial, the entire stock of investigational products remaining in possession of the investigator will be immediately withdrawn from locations where these were dispensed and notified on to the relevant general directorate within fifteen days, with supporting documentation as a report.
(2) The withdrawal of investigational products, and particulars of the process and precautions taken with respect to the withdrawn investigational products will be detailed in the report submitted to the relevant general directorate.

CHAPTER SEVEN
Reporting of Adverse Events and Serious Adverse Effects

Reporting of adverse events
ARTICLE 24 – (1) All adverse events mentioned in the protocol or the investigator's brochure or adverse events occurring during the clinical trial and deemed as not requiring immediate reporting will be reported to the relevant ethics committee and the general directorate concerned within the timeframes specified in the protocol.
(2)The investigator will report all serious adverse events immediately to the sponsor. The sponsor is obligated to urgently report to the Ministry on this information. The sponsor will submit a detailed report on serious adverse events to the relevant ethics committee and the general directorate concerned within eight days. In the urgent report and in any follow-up reports, a single code number will be used for volunteers participating in the study.
(3) Adverse events and/or laboratory findings identified as critical to safety evaluations will be immediately reported to the sponsor in the manner and timelines mentioned in the protocol.

(4) In the event of death of a volunteer, the investigator will supply the sponsor, the relevant ethics committee, and the general directorate concerned with any additional information as requested.
(5) The sponsor will keep detailed records of all adverse events reported to it by the investigator or investigators. These records will be submitted to the general directorate concerned, if they so request.

Reporting of serious adverse events
ARTICLE 25 – (1) The sponsor will ensure that all relevant information about suspected serious unexpected adverse effects that are fatal or life-threatening is reported to the relevant ethics committee and the general directorate concerned, immediately after receiving such information. Relevant follow-up reports containing additional information on the cases will be subsequently communicated to the same authority within eight days (two days for medical devices) after receiving such information.
(2) All other unexpected serious adverse effects will be reported by the sponsor to the relevant ethics committee and the general directorate concerned, within fifteen days (seven days for medical devices) after having first knowledge of this information. The sponsor will also inform all investigators.
(3) Once a year, the sponsor will provide the relevant ethics committee and the general directorate concerned with a listing of all suspected serious adverse effects, including information relevant to volunteers' safety, using the interim report form provided in the relevant guidelines to be issued by the Ministry. In short-term studies or where necessary, the general directorate may request a report earlier.

Other notifications
ARTICLE 26 – (1) In multi-center trials, the interim report and the final report, prepared using a template of the forms provided in relevant guidelines, will include the relevant results from all centers taking part in the trial.
(2) Notification to ethics committee and the Ministry is sufficient for the appointment of sub-investigators, site coordinators or monitors by the sponsor. However, the Ministry may void such appointments by giving a reason.
(3) The responsibility to ensure regular submission of the notifications to the relevant general directorate rests with the sponsor.

CHAPTER EIGHT
Miscellaneous and Final Provisions

Training
ARTICLE 27 – (1) The Ministry may hold courses or seminars to develop qualified investigators, health personnel and other individuals working in the field who are well-trained in good clinical practice; the Ministry will also inspect courses or seminars organized by pharmaceutical or medical device companies, and approve ones which have curriculums acceptable to the Ministry.

Clinical trial records and confidentiality
ARTICLE 28 – (1) All records related to the clinical trial will be regularly kept by sponsor and investigator, and maintained for not less than five years after the study is completed at all

centers. In the case of implantable devices, the record retention period is not less than fifteen years. In the case of clinical trials involving cells or tissues, the records must be retained for not less than thirty years. Archiving of essential documents must permit convenient retrieval upon the request of a competent authority.
(2) The Ministry must be notified in the event of transfer of the clinical trial for any reason. The new owner is responsible to maintain and archive all of the data and documents.
(3) Confidentiality of documents related to a clinical trial is essential. These documents are disclosed to authorized parties only upon the request of legally authorized persons or bodies.

Inspection
ARTICLE 29 – (1) Clinical trials being conducted, trial sites, sponsors and contract research organizations, manufacturing sites of investigational products, laboratories where analyses relevant to the trial are being performed, and ethics committees mentioned in Article 10 herein is inspected in and/or outside of the country by the Ministry, with or without advance notice, to determine compliance with this Regulation and other applicable regulatory provisions.
(2) Inspectors of good clinical practice will be appointed among doctors of medicine, pharmacists or other individuals with a bachelor's degree in a relevant branch who have sufficient experience and training in good clinical practice.
(3) Inspectors of good clinical practice are obligated to maintain confidentiality of all information they acquire during inspection.

Responsibility
ARTICLE 30 – (1) The entire civil and financial liability in connection with a clinical trial rests with the individual, organization/institution conducting the trial, the sponsor, and the contract research organization. However, in the case of clinical trials funded by institutions or organizations such as the Ministry of Development, TÜBİTAK, or universities, the entire civil and financial liability in connection with the clinical trial rests with the principal investigator.
(2) The costs of all investigational medicinal products, devices or materials dedicated for using the products, and the costs of all examinations, tests, analyses and treatments used in the trial will be covered by the sponsor. Such costs are not be recovered from volunteers or from social security institutions, with or without the knowledge and consent of volunteers. Invoices and other documentations showing that these costs were paid by the sponsor will be retained by the sponsor, and must be submitted upon the request of the Ministry and/or during inspections by the Ministry or other competent authorities, organizations or institutions.
(3) The cost of standard examinations, tests, analyses and therapies used in clinical trials conducted for academic purposes, including theses of medical residents, will be covered by social security institutions, upon the prior knowledge and approval of such institutions. The responsibility for all other costs rests with the study sponsor.
(4) Natural or juristic persons who are to conduct a clinical trial must detail the particulars of trial funding in the application dossier. However, if the project is funded by local/foreign institutions or organizations such as the Ministry of Development, TÜBİTAK or universities, and if the project's funding is clarified with its acceptance by these institutions or organizations, it is sufficient to indicate this on the clinical trial application form and it is not necessary to itemize the particulars of funding. However, when the project is accepted, the particulars of funding will be submitted in an additional communication to the relevant ethics committee or the general directorate concerned, by the person, institution or organization responsible for correspondence.
(5) The fact that a Volunteer Informed Consent Form has been obtained from volunteers participating in a clinical trial will not annul such volunteers' entitlement to seek compensation of damages experienced by them in connection with the trial.

Prohibitions
ARTICLE 31 – (1) It is prohibited to publish results from a clinical trial falling within the scope of this Regulation where the conduct of such clinical trial has been inconsistent with this Regulation and/or the procedures and principles provided in other applicable regulations.
(2) Ethics committee members do not attend committee meetings, nor they undersign any decision taken, unless they sign the confidentiality paper and the letter of commitment.
(3) Ethics committee members are prohibited from disclosing any data or documents that they have been granted access in connection with a clinical trial. Such data and documents will be disclosed solely to authorized parties, upon the request of legally authorized persons or authorities.

Regulatory penalties and penal sanctions
ARTICLE 32 – (1) Whoever violates or acts contrary to these regulatory provisions will be subjected to applicable provisions of the Turkish Penal Code numbered #5237 and dated 26/09/2004 and other relevant regulations, depending on the nature of the violation.
(2) In the event of violation of regulatory provisions governing clinical trials, the offending clinical trial, or in the case of international multi-center clinical trials, the part of the study being conducted in Turkey, may be suspended or terminated by the Ministry. When the reasons for suspension have been addressed, the sponsor notifies the Ministry and the clinical trial may be resumed, if approved by the Ministry.

Guideline
ARTICLE 33 – (1) The guidelines to provide guidance for the implementation of this Regulation will be issued by the Ministry, and such guidelines, after they are published, will be enforced together with this Regulation.

Conditions with no provision
ARTICLE 34 – (1) Conditions not provided in this Regulation will be governed according to the provisions of Law #5013 of 03.12.2003 Ratifying the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine and the Convention on Human Rights and Biomedicine; the Medical Deontology Regulation put into force by Cabinet of Ministers' Decree numbered #4/12578 and dated 13/01/1960; the provisions concerning the rights of volunteers taking part in a study as provided in the Regulation on Patient Rights, published in the Official Gazette numbered #23420 and dated 01/08/1998; and other applicable regulatory provisions.

Superseded regulation
ARTICLE 35 – (1) The Regulation on Clinical Trials, published in Official Gazette numbered #27089 and dated 23/12/2008, is hereby superseded.

Effectiveness
ARTICLE 36 – (1) This Regulation will enter into force on the date it is published.

Enforcement
ARTICLE 37 – (1) Provisions of this Regulation will be enforced by the Minister of Health.