**REGULATION**

By Turkish Medicines and Medical Devices Agency:

# REGULATION ON CLINICAL TRIALS OF MEDICINAL AND BIOLOGICAL PRODUCTS

## CHAPTER ONE
## Purpose, Scope, Basis and Definitions

**Purpose**

**ARTICLE 1 –** (1) This Regulation sets forth principles and procedures for conducting scientific research in humans and protecting rights and interests of research subjects in accordance with good clinical practice, standards of the European Union, and international conventions to which Turkey is a party, and lays down principles and procedures for the establishment, mandate and operation of an Advisory Committee for Clinical Trials and ethics committees.

**Scope**

**ARTICLE 2 –** (1) This Regulation applies to clinical trials conducted in humans, including studies to investigate bioavailability and bioequivalence, with drugs, medicinal and biological products, or herbal medicinal products, whether authorized or licensed, as well as the centers where clinical trials are conducted, and the natural or juristic persons who conduct them.

(2) This Regulation does not apply to retrospective studies.

**Basis**

**ARTICLE 3 –** (1) This Regulation is issued based on Supplemental Article 10 of Fundamental Law #3359 dated 07.05.1987 on Health Services and Articles 27 and 40 of Decree Law #663 on the Organization and Mandate of the Ministry of Health and Its Subordinate Agencies, and is aligned with Directives 2001/20/EC and 2005/28/EC concerning Good Clinical Practice, constituting a part of European Union's legislations governing medicinal products.

**Definitions**

**ARTICLE 4 –** (1) For the purposes of this Regulation the following definitions apply:

a) Adverse event: any untoward medical occurrence in a clinical trial subject, which does not necessarily have a causal relationship with the administered treatment;

b) Adverse reaction: all untoward and unintended responses occurring in a clinical trial subject;

c) Investigator: a person involved in a clinical trial under the supervision of a principal investigator;

ç) Investigator's brochure: a compilation of clinical and non-clinical data on the investigational medicinal product and its administration;

d) Study protocol: a document that details the objectives, design, methodology, statistical methods to be used, and organization of a clinical trial.

e) Investigational medicinal product: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial;

f) Relative bioavailability: bioavailability as compared with another form administered by the same or another non-intravenous route which provides higher bioavailability;

g) Ministry: the Ministry of Health;

ğ) Unexpected serious adverse reaction: any serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information;

h) Subject's informed consent form: a documented proof of consent, given based on detailed and comprehensible information about the study;

ı) Bioequivalence: the state of two products' being pharmaceutically equivalent and their bioavailabilities' after administration in the same molar dose being similar to such degree that their effects, with respect to both efficacy and safety, are essentially the same;

i) Bioavailability: the rate and extent to which an active substance or active moiety is absorbed from a pharmaceutical form into systemic circulation and becomes available at the site of action or in representative biological fluids, generally serum and plasma;

j) Serious Adverse Event or Serious Adverse Reaction: any adverse event or reaction 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;

k) Multicenter Clinical Trial: a clinical trial conducted according to a single protocol but at more than one site, and is, therefore, involving more than one principal investigators;

l) Audit: an act by the Agency of auditing sites where a clinical trial is conducted, the centers owned by sponsors or contract research organizations, study-related documents and records, quality assurance arrangements and other organizations,

boards or institutions related to the study, including ethics committees, for compliance with this Regulation or other applicable regulations;

m) Sponsor: an individual, institution or organization who takes responsibility for the initiation, conduct and/or funding of a clinical trial;

n) Ethics committee: a body established with the approval of the Agency to protect the rights, safety and wellbeing of human subjects by, among other things, expressing their scientific and ethical opinion on the methods and documents to be used to inform trial subjects and obtain their informed consent;

o) Subject: 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, given according to this Regulation and other applicable regulations,

ö) Observational drug study: an epidemiological study to collect data on a medicinal product, spontaneously prescribed to patients undergoing treatment in the indications using the posology and route of administration, for which the product has been approved in Turkey according to the current diagnostic and therapeutic guidelines of the Ministry;

p) Drug or medicinal product: any natural, synthetically or biotechnologically derived active substance or combination of substances administered to humans with a view to curing, preventing or diagnosing a disease, or correcting, regulating or modifying a physiological function;

s) Good clinical practice: the rules that must be followed by all 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 research is conducted according to international scientific and ethical standards, for protecting the rights and physical integrity of subjects, ensuring reliability and confidentiality of study data;

ş) Disabled: any person who meets the criteria for disability as described in Turkish Civil Code #4721 of 22.11.2001;

t) Clinical trial: any investigation in humans intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or to identify any adverse reactions to one or more investigational medicinal products or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining their safety and efficacy;

u) Advisory Board for Clinical Trials: a council to be formed for expressing an opinion on matters related to clinical trials;

ü) Agency: Turkish Medicines and Medical Devices Agency;

v) Absolute bioavailability: bioavailability of the same molar quantity of a product as compared with that following intravenous administration;

y) Principal investigator: a physician or dental practitioner holding a doctorate or medical residency degree in a relevant branch, taking responsibility for the conduct of the study;

z) Contract research organization: an independent organization operating according to good clinical practice to whom the sponsor has delegated all or some of its duties and powers in connection with the clinical trial by a written contract.

aa) Administrative Responsible Person: A person, preferably holding a doctoral or medical residency degree, who is responsible for the coordination between principal investigators of trial sites and the ethics committee and the sponsor, or its legal representative, and, when necessary, between these parties and the Agency, on matters related to administrative aspects during the course of study in a multi-center trial setting.

bb) Legal representative: A person authorized to consent to enrollment in a clinical trial, for and on behalf of a potential subject, in line with the applicable regulations.

cc) Coordinator: A physician or dental practitioner, preferably holding a medical residency or doctoral degree, who is responsible for coordination between principal investigators of trial sites and the ethics committee and the sponsor or its legal representative, and, when necessary, between these parties and the Agency, in a multi-center trial setting."

## CHAPTER TWO
## General Principles for Trials, Obtaining Approval for a Trial

**General principles for trials**

**ARTICLE 5 –** (1) The following requirements apply for conducting a trial with subjects:

a) The study has been performed first in a non-human in vitro environment or in a sufficient number of test animals.

b) Scientific data obtained in a non-human in vitro environment or from experiments in animals are, as far as the study objectives are concerned, sufficient to warrant conducting the study in humans also.

c) The benefits for science and the society expected from a trial must not prevail over the personal rights or good health of the subjects involved in the trial, or over any potential risks to their health.

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

d) Decisions related to the medical follow up and treatment of a study subject will be taken by a physician or dental practitioner professionally qualified to take such decisions.

e) Any procedures that inflict pain on the subject to a degree that would be incompatible with human dignity are prohibited.

f) The study design should minimize pain, discomfort, fear, and any risks related to the patient's condition or age. Both the limit of risk and the degree of discomfort must be specifically defined and continuously monitored.

g) The purpose of the trial must outweigh the burden placed on the person and the risk to the person's health.

ğ) It is essential that the study does not have any foreseeable noxious or permanent effects on human health.

h) Where it is concluded by the ethics committee that the anticipated benefits of a trial outweigh the potential risks, the trial may be initiated, having obtained the Agency's approval, provided the consent of the subjects is obtained in line with the applicable procedure and with due regard for their personal rights. The trial may only be continued for as long as these conditions are met.

ı) Prior to participation in the trial, the subject, or the subject's legal representative, will be informed by the principal investigator or by an investigator who is also a physician or dental practitioner fully knowledgeable in the subject matter of trial, sufficiently and in a manner comprehensible to the subject or the subject's legal representative, on the objective, methodology, expected benefits, foreseeable risks, challenges, and any aspects unfavorable to the subject's health or personal characteristics, as well as the conditions under which the study will be conducted and carried out, and that the subject is free to withdraw from the trial whenever the subject so wishes.

i) The subject's consent will be obtained that he or she will be participating in the trial by his or her completely free will, and this will be documented on a Subject's Informed Consent Form covering the information described in paragraph (ı) above.

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

k) Subjects may withdraw from the trial at discretion, with or without giving a reason, at any time of their choosing, and may not be deprived of any of their rights during subsequent medical follow up and treatment.

l) To secure the subjects against harms from the clinical trial, insurance meeting regulatory requirements must be provided to subjects who take part in clinical trials, except observational drug studies and Phase IV clinical studies specified in Article 10, Paragraph (ç). However, for non-drug clinical trials, this will be determined based on the nature of the clinical trial. However, for non-drug clinical trials, this will depend on the nature of the study.

m) No compelling incentive and/or financial benefit, except insurance coverage, may be provided to encourage subjects or their legal representatives to participate or remain in the study. However, expenses associated with subjects' participation in the trial and any reduction in the personal income of healthy subjects resulting from workday loss will be specified and covered in the trial budget.

n) Subject identification details will not be disclosed when publishing the results from a clinical trial.

**Children's participation in a trial**

**ARTICLE 6 –** (1) Where the subject matter of research 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 study in children within the below premise, taking account of the considerations highlighted above in Article 5, provided that the study carries no foreseeable risk to subjects' well-being and there is a common medical view that the study will directly benefit the subjects:

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

b) If the child is capable of expressing consent, written consent of the child's parents, or custodian, where applicable, must be also obtained, in addition to the child's consent, after being informed according to Article 5, Paragraph 1, Subparagraph (ı).

c) The child will be removed from the trial immediately if he or she wishes to withdraw from the study at any stage, or refuses to take part in it.

ç) If the child is capable of weighing the information provided and reaching a sound decision, all relevant information regarding the trial will be explained to the child using appropriate language.

d) The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a pediatrician who holds a doctoral or medical residency degree in pediatric dentistry, and give consideration to the protocol accordingly.

e) An ethics committee may not approve any clinical trial in children unless a favorable view for conducting the study in children has been given by a pediatrician. If deemed necessary for these trials, the opinion of a pediatrician or a pediatric dentist holding a doctoral or medical residency degree in a field relevant to the subject matter of the trial will be consulted, and the decision on whether or not to authorize the trial will be based on such opinion.

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

**Participation of pregnant, puerperal or breastfeeding women in a trial**

**ARTICLE 7 –** (1) Where the subject matter of research is directly related to pregnant, puerperal or breastfeeding women or is a clinical condition that can be investigated only in pregnant, puerperal or breastfeeding women, it may be

permitted to conduct a study in pregnant, puerperal or breastfeeding women within the below premise, taking account of the considerations highlighted above in Article 5, provided that the study carries no foreseeable risk to subject and fetal/infant health and there is a common medical view that the study will directly benefit the subjects:

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

b) Written consent of the pregnant, puerperal or breastfeeding woman must be obtained, after being informed according to Article 5, Paragraph 1, Subparagraph (ı).

c) A pregnant, puerperal or breastfeeding woman will be immediately removed from the trial if they wish to withdraw from the study at any stage, or refuses to take part in it.

ç) The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial, particularly with regard to fetal or infant health, by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.

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

**Participation of disabled persons in a trial**

**ARTICLE 8 –** (1) Where the subject matter of research is directly related to disabled persons or is a clinical condition that can be investigated only in disabled persons or all existing therapy options to treat the disabled person's condition have been exhausted, it may be permitted to conduct a study in them within the below premise, taking account of the considerations highlighted above in Article 5, provided that the study carries no foreseeable risk to subject health and there is a common medical view that the study will directly benefit disabled subjects:

a) A common medical view must exist that the investigational product or procedure carries no known risk to disabled persons.

b) If the person is capable of consent, his or her written consent must be obtained with that of the custodian, after being informed according to Article 5, Paragraph 1, Subparagraph (ı).

c) If the disabled person is capable of weighing the information provided and reaching a sound decision, they must be removed from the trial immediately if they wish to withdraw from the study at any stage, or refuse to take part in it.

ç) The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.

d) No compelling incentive or financial benefit may be offered in connection with a clinical trial in disabled persons, other than covering obligatory expenses arising from their participation in the trial.

**Trial participation of persons unconscious or in intensive care**

**ARTICLE 9 –** (1) Where the subject matter of research is directly related to persons unconscious or in intensive care, or is a clinical condition that can be investigated only in persons unconscious or in intensive care or all existing therapy options to treat their condition have been exhausted, it may be permitted to conduct a study in persons unconscious or in intensive care within the below premise, taking account of the considerations highlighted above in Article 5, provided that the study carries no foreseeable risk to subject health and there is a common medical view that the study will directly benefit persons unconscious or in intensive care:

a) A common medical view must exist that the investigational product or procedure carries no known risk to persons unconscious or in intensive care.

b) Written consent must be obtained of legal representatives or relatives of persons unconscious or in intensive care after being informed according to Article 5, Paragraph 1, Subparagraph (ı).

c) If a person unconscious or in intensive care becomes capable of weighing the information provided to them and reaching a sound decision, they must be removed from the trial immediately if they wish to withdraw from the study at any stage, or refuse to take part in it.

ç) The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.

d) No compelling incentive or financial benefit may be offered in connection with a clinical trial in persons unconscious or in intensive care, other than covering obligatory expenses arising from their participation in the trial.

(2) In the event a person unconscious or in intensive care or their legal representative or relatives cannot be reached to obtain their written consent, persons unconscious or in intensive care may be included in a trial, under the responsibility of the principal investigator or an investigator who is a medical doctor, provided the prescriptions of paragraph one above and the following requirements have been met:

a) The ethics committee must have given consideration to the proposed study protocol and other pertinent documents to determine whether the trial in question sufficiently meets ethical requirements.

b) In cases occurring suddenly, requiring urgent medical intervention and where existing therapy options have been completely exhausted, there is common medical view that the study will directly benefit persons unconscious or in intensive care.

## CHAPTER THREE
## Essentials for Conducting a Trial

**Phases of clinical trials**

**ARTICLE 10 –** (1) Clinical trials have the following phases:

a) Phase I or Period I: Represents the stage of clinical research wherein an investigational product is investigated by administering it to a sufficient number of healthy subjects, or to unhealthy subjects when it is impossible to work with healthy subjects, who have been selected according to the nature and character of the study, to evaluate its pharmacokinetics, toxicity, and effects on physiological functions. A Phase I or Period I clinical trial with a novel investigational product may not be initiated unless preclinical pharmacological, toxicological and similar studies have been performed using complete and suitable experimental methods.

b) Phase II or Period 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 or Period III: Represents the stage of clinical research wherein an investigational product, having passed through Phases I and II, 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 or Period IV: Represents the stage of clinical research in a large number patients where products authorized in Turkey are further investigated in terms of their approved indications, posology, and method of administration , 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 11 –** (1) Clinical trials may only be conducted at centers for health practice and research established within universities, approved centers for research and development within universities and teaching and research hospitals of the Ministry, including Gülhane Military Medical Academy and military teaching and research hospitals, preferably at locations dedicated to clinical research, which are suitable for and which 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. Where necessary, other healthcare institutions or organizations, possessing the above-listed capabilities, may be included in clinical trials conducted at these centers or hospitals, under the coordination or administrative responsibility of the latter.

(2) Phase I clinical trials and bioavailability/bioequivalence studies are conducted at healthcare institutions and research and development centers approved by the Agency, subordinate to the Ministry or universities, and equipped with the necessary means to perform emergency interventions when necessary and meeting standards set individually for each of them.

(3) Sites where clinical trials will be conducted according to 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 subjects, including cases requiring emergency care,

ç) the sufficient means and equipment to enable transferring subjects 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 subjects after the study has been completed.

**Clinical trial application and authorization**

**ARTICLE 12 –** (1) Making a parallel application to the ethics committee and the Agency simultaneously is allowed, to obtain authorization for conducting a clinical trial falling within the scope of this Regulation.

(2) The application file 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 appendixes posted on the Agency's website.

(3) The said Ethics Committee decision must be obtained from the Ethics Commitee based at the place where the coordinating center is situated or, if no Ethics Committees are available there, from the Ethics Committee based at the center nearest to the coordinating center. For clinical trials conducted at a single center, the required Ethics Committee decision must be obtained from the Ethics Commitee based at the place where the trial is being conducted or, if no Ethics Committees are available there, from the Ethics Committee based at the center nearest to the said center.

(4) The application for a clinical trial will be made to the relevant ethics committee and the Agency by the sponsor, consisting of natural/juristic persons, 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.

(5) If the application has been submitted in a procedurally correct manner, there are no deficiencies in the data or documents which must be submitted with the application, and an ethics committee decision is available and submitted, it is essential for the Agency to review and conclude the application within thirty days.

(6) If the Agency 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. The review clock will be paused during this process. If the requested changes are not made or an acceptable justification cannot be presented, the Agency may reject the clinical trial.

(7) For clinical trials with cell therapies using products containing genetically modified organisms or products involving gene therapy, the timeframe specified for the Agency approval may be extended for an additional thirty days.

**Initiating and conducting a clinical trial**

**ARTICLE 13 –** (1) Clinical trials subject to the Agency's approval may not be initiated without the Agency's approval. These studies will be entered in a public register, respecting the privacy of personal information.

(2) Amendments occurring during conduct of a trial requiring reporting, and those requiring a decision and approval will be determined according to the Guideline for Good Clinical Practice. It is essential for amendments requiring a decision and approval to be reviewed and concluded by the ethics committee within fifteen days, and by the Agency within thirty days after submission of the ethics committee decision.

(3) Trials will be conducted in the following manner:

a) Clinical trials subject to this Regulation will be conducted with a team appropriate to the nature of the study, led by a principal investigator. Phase I clinical trials and bioavailability/bioequivalence trials will be conducted by a team with sufficient training and experience in good clinical practice and a doctor of medicine specialized or holding a doctoral degree in pharmacology.

b) Reserving the provisions made in the second paragraph above, the sponsor or the principal investigator or the physician or an investigator who is a dental practitioner will take any urgent safety precautions necessary to protect subjects against risks 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 subjects' safety. The principal investigator or the sponsor will notify the relevant ethics committee and the Agency on these new circumstances and the precautions taken. Otherwise, the Agency will suspend the study.

c) If, despite approval by the Agency, a study has not been initiated on the date specified in the application file, reasons for not initiating the study will be reported to the Agency within ninety days.

ç) In order to ensure the conditions and precautions necessary for the safety of patients, the principal investigator may recruit subinvestigators 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 Agency. Delegation of duties to a contract research organization will not annul a 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 14 –** (1) The Agency 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 subjects' safety will be compromised in the mean time, the clinical trial will be directly suspended.

(2) In cases not involving a direct risk to subjects, the sponsor or investigator may be requested to submit their view on the issue. In that case, the sponsor or investigators will submit their view to the Agency within fifteen days.

(3) If a trial has been prematurely stopped by the sponsor, the decision to stop the trial, including the reasons for stopping it and a description of measures to maintain treatment of subjects already enrolled in the study, will be submitted to the Agency and the ethics committee within fifteen days.

(4) The sponsor will report the end of trial to the Agency and the ethics committee within ninety days after the trial ends.

(5) The decision and the rational for stopping or terminating a clinical trial will be notified to the ethics committee, the sponsor and the principal investigator.

## CHAPTER FOUR
## Investigational Products

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

**ARTICLE 15 –** (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.

(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 or the study protocol, checking the inventory, and following the protocol requirements for and keeping a record of any remaining products. The principal investigator may appoint, preferably, a pharmacist to perform these functions.

**Manufacture, importation, and labeling of investigational products**

**ARTICLE 16 –** (1) It must be assured that investigational products have been manufactured in accordance with the requirements laid won in the Guideline for Good Manufacturing Practice.

(2) Permission of the Agency will be obtained for importing or manufacturing investigational products.

(3) Sponsors who intend to manufacture or import an investigational product must meet the following requirements:

a) The application made to the Agency 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 relevant data and documents, must be retained for at least five years.

(4) Investigational products 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.

**Withdrawal of investigational products**

**ARTICLE 17 –** (1) In the event of suspension of a clinical trial, the entire stock of investigational products remaining in possession of the principal investigator or an investigator who is a medical doctor or dental practitioner will be immediately withdrawn from locations where these were dispensed and reported on to the Agency within fifteen days, with supporting documentation.

(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 Agency.

## CHAPTER FIVE
## Reporting Adverse Events and Serious Adverse Reactions, Other Notifications, Audits and Responsibility

**Reporting adverse events**

**ARTICLE 18 – (**1) The principal investigator or an investigator to be assigned by the principal investigator will notify the sponsor immediately about all adverse conditions other than those that are not require immediate reporting as specified in the protocol or the investigator's brochure. This urgent report will then be followed by a detailed written report. A single code number will be used in the urgent report and other subsequent reports for volunteers participating in the study.

(2) Adverse events or laboratory findings identified as critical to safety evaluations will be reported to the sponsor in the manner and timelines described in the protocol.

(3) In the event of death of a subject, the principle investigator or an investigator appointed by the principal investigator will supply the sponsor, the relevant ethics committee, and the Agency with any additional information requested.

(4) 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 Agency and the ethics committee upon request.

**Reporting serious adverse reactions**

**ARTICLE 19** – (1) The sponsor will inform the ethics committee and the Agency about any fatal or life-threatening suspected unexpected serious adverse reactions occurring during the trial within no more than seven days after receiving such information. The sponsor will also forward any follow-up reports containing additional information on these cases to the ethics committee and the Agency within eight days after receiving them.

(2) All the other unexpected suspected serious adverse reactions will be reported to the ethics committee and the Agency by the sponsor within a maximum of fifteen days after receiving the initial information.

(3) The sponsor will also notify all investigators and the principal investigator.

(4) Once a year, the sponsor will provide the ethics committee and the Agency with a listing of all suspected serious adverse reactions occurring during the trial, including information relevant to subjects' safety, using the interim report form provided in the relevant guidelines to be issued by the Agency. In short-term studies or where necessary, the Agency may request a report earlier.

**Other notifications**

**ARTICLE 20 –** (1) In multicenter clinical trials, the interim report and the final report will be prepared using a template of the forms provided in relevant guidelines and on the Agency's website, and include the relevant results from all centers taking part in the trial.

(2) Appointments related to the trial that require reporting, and those requiring a decision and approval will be determined according to the Guideline for Good Clinical Practice. However, the Agency may invalidate appointments subject to reporting, stating a reason therefor.

(3) It is the sponsor's responsibility to ensure that notifications are regularly submitted to the Agency.

**Trial records, confidentiality and transfers**

**ARTICLE 21 –** (1) All records related to the clinical trial will be regularly kept by sponsor and the principal investigator or investigators, and maintained for at least five years after the study has been completed at all centers.

(2) The sponsor will notify the ethics committee and the Agency in the event of transfer of the trial for any reason. The Agency approves the transfer, if it finds it acceptable. In the event of a transfer of trial, the new owner of the data and documents is responsible to maintain and archive all of them.

(3) Archiving of trial data and documents must be compliant with the applicable guideline.

(4) Confidentiality of trial data and documents is essential. These documents may be only disclosed upon request by to legally authorized persons or authorities.

**Audits**

**ARTICLE 22 –** (1) The Agency may audit 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 in and/or outside of the country, with or without advance notice, to determine their compliance with this Regulation and other applicable regulatory provisions.

(2) Auditors will be appointed among persons, preferably with an educational background in medicine or pharmacy and holding a bachelor's degree, who have sufficient experience and training in good clinical practice

(3) Good clinical practice auditors are obligated to maintain confidentiality of all information they acquire during inspection.

**Responsibility**

**ARTICLE 23 –** (1) The cost of all investigational medicinal products, devices or materials for use with the products, and the costs of all examinations, tests, analyses and treatments used in the trial and specified in the Agency-approved study protocol will be covered by the sponsor. Such costs may not be recovered from subjects or from the Social Security Institution. However, this excludes situations involving a public interest and approved by the Social Security Institution.

(2) Natural or juristic persons who will be conducting the clinical trial must detail the particulars of study funding in the application dossier.

(3) That a Subject's Informed Consent Form was obtained from subjects enrolled in a clinical trial will not their entitlement to seek compensation for damages sustained by them in connection with the trial.

**Prohibitions**

**ARTICLE 24 –** (1) It is prohibited to conduct trials covered by this Regulation in a manner that violates the principles and procedures laid down in this Regulation or other applicable legislations.

**Regulatory penalties**

**ARTICLE 25 –** (1) 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 Agency. When the reasons for suspension have been eliminated, the sponsor notifies the Agency and the clinical trial may be resumed, if approved by the Agency.

(2) The Agency will issue a warning to ethics committees which do not operate according to ethical principles or fail to meet the requirements of the Standard Operating Procedure for Ethics Committees issued by the Agency, or found during audits to lack the essential space, secretariat, archive and other equipment means which are required for an ethics committee to function. If the deficiencies giving rise to the warning are not rectified within the allowed timeframe, the Agency will revoke the authorization granted according to Article 26, paragraph 2, and remove the chair of the ethics committee for a period of two years.

(3) Whoever violates or acts contrary to these regulatory provisions will be subjected to applicable provisions of the Turkish Penal Code #5237 of 26.09.2004 and other relevant regulations, depending on the nature of the violation.

## CHAPTER SIX
## Organization, Operating Principles and Procedures, and Duties of Ethics Committees

**Organization of ethics committees**

**ARTICLE 26 –** (1) Ethics committees are comprised of not less than seven and not more than fifteen members, all healthcare professionals who received basic training on clinical trials and a majority of whom holding a doctoral or medical residency degree, to conduct scientific and ethical assessments on various matters, including procedures and documents used to inform trial subjects and consents received from them, to protect their rights, safety and wellbeing.

(2) Ethics committees will be established within universities upon the proposal of the rector, within Public Hospital Unions upon the proposal of the secretary general, and within Gülhane Military Medical Academy upon the proposal of the dean and confirmation by the Agency, and commence their work as of the confirmation date.

(3) Ethics committees will be organized as an Ethics Committee for Clinical Research or an Ethics Committee for Bioavailability/Bioequivalence Investigation.

(4) Ethics Committees for Clinical Research will be established to perform a scientific and ethical assessment of studies except bioavailability/bioequivalence studies.

(5) Ethics Committees for Bioavailability/Bioequivalence Investigation will be established to perform scientific and ethical assessment of bioavailability/bioequivalence studies.

(6) At least three members of an ethics committee will be selected from outside the institution where the committee's secretariat is located.

(7) An ethics committee member may not sit on more than one ethics committees.

(8) Senior executives of clinical research sites may not sit on ethics committees.

(10) Members of an Ethics Committee for Clinical Research must meet at least the following qualifications:

a) Specialist physicians who have previously taken part as an investigator in an international clinical trial conducted preferably according to good clinical practice, who are preferably specialized in different branches;

b) A person holding a doctoral or medical residency degree in pharmacology;

c) A person holding a doctoral degree in biostatistics or a public health specialist or a medical doctor holding a doctoral degree in public health;

ç) A biomedical engineer or specialist, or, if unavailable, a biophysicist or physiologist;

d) A jurist;

e) A non-healthcare professional;

f) If available, a person holding a doctoral degree or specialized in medical ethics or deontology;

(11) Members of an Ethics Committee for Bioavailability/Bioequivalence Investigation must meet at least the following qualifications:

a) Specialist physicians who have previously taken part as an investigator in an international clinical trial conducted preferably according to good clinical practice;

b) A person holding a doctoral or medical residency degree in pharmacology;

c) A person holding a doctoral degree in biostatistics or a public health specialist or a medical doctor holding a doctoral degree in public health;

ç) A pharmacist holding a doctoral degree in biopharmaceuticals, pharmacokinetics or pharmaceutical technology ;

d) A pharmacist holding a doctoral degree in pharmaceutical chemistry or analytical chemistry, or a chemist or chemical engineer holding a doctoral degree in said fields;

e) A jurist;

f) A non-healthcare professional,

g) If available, a person holding a doctoral degree or specialized in medical ethics or deontology.

**Operating principles and procedures of ethics committees**

**ARTICLE 27 –** (1) Operating guidelines and procedures of ethics committees are outlined below:

a) Ethics committees are independent in their scientific and ethical review and approval of clinical trial applications.

b) Ethics committee members are obligated to comply with the confidentiality requirement for any information presented to them.

c) Ethics committee members will sign a confidentiality form and letter of undertaking before commencing their role.

ç) Ethics committee members who are affiliated with or have a role in the trial being reviewed may not take part in discussions or voting on such trial at the ethics committee, nor may they have their signature under the ethics committee decision thereon.

d) Ethics committee members meet with two thirds majority of the total number of members, and adopt decisions with absolute majority of total membership.

e) Ethics committee members serve for two years, and an expiring member may be reappointed.

f) Any members who fail to attend three consecutive or five nonconsecutive meetings without a valid excuse during their membership term will be automatically removed from membership. Members who expire their term or otherwise removed from membership are replaced by a new member meeting, preferably, the same qualifications, for members other than those who must be present at minimum.

g) Where necessary, ethics committees may solicit the written opinion of experts in a relevant field or subfield, and invite them to attend meetings in advisory capacity.

ğ) Operating modalities of ethics committees are set by the Agency and posted on the Agency's website. Ethics committees conduct their work in adherence to those standards.

**Mandate of ethics committees**

**ARTICLE 28 –** (1) Ethics committees have the following mandate:

a) Applications for clinical trials falling within the scope of this Regulation will be reviewed by an ethics committee according to Article 26.

b) Other agencies or institutions may not establish ethics committees or any boards or organs to serve the function of an ethics committee to review matters falling within the scope of this Regulation.

c) When forming their opinion on a clinical trial application, ethics committees will at least 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) the study protocol;

6) an evaluation of the contents of the investigator's brochure and whether it meets the requirements;

7) the documented information submitted relating to the study, the method used for obtaining the consent of subjects, and the justification for conducting the study in pregnant, postpartum or breastfeeding women, children, disabled persons or persons who are unconscious or in intensive care;

8) the responsibility of the principal investigators or the sponsor in the event of injury or death, including permanent health problems which may potentially result from the study;

9) compensation in the event of an injury or death which may be linked with the study;

10) arrangements for including subjects in the study;

11) suitability of the trial team for the type of study being conducted.

ç) Ethics committees may perform on-site audits during trials approved by them.

d) Ethics Committees for Clinical Research will notify their opinion to the applicant within not more than fifteen days, and Ethics Committees for Bioavailability/Bioequivalence within not more than seven days after the application date.

e) In the case of non-drug clinical trials and clinical trials with cell therapies using products containing genetically modified organisms or products involving gene therapy, the fifteen-day timeframe specified for ethics committee approval may be extended for an additional thirty days.

f) 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. The review process will be frozen until the required data and documents are submitted to the ethics committee.

## CHAPTER SEVEN
## Organization and Operating Principles and Procedures of the Advisory Board for Clinical Trials, Observational Drug Trials and Training

**Organization of the Advisory Board for Clinical Trials**

**ARTICLE 29 –** (1) The Advisory Board for Clinical Trials will be chaired by the Undersecretary of Health or a Deputy Undersecretary appointed by him or her, and comprise three members each selected by the Agency specialized or holding a doctoral degree in surgery, internal medicine and basic sciences, respectively, a clinical psychologist and theologist, and the Agency's Chief Legal Advisor, or a legal advisor appointed by him or her.

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

**ARTICLE 30 –** (1) The Advisory Board for Clinical Trials will perform the following duties:

a) Providing its scientific and technical opinion solely on matters referred to the Agency in writing for opinion on matters of indecision by an ethics committee regarding a clinical trial.

b) Providing its opinion solely on matters referred to the Agency in writing for opinion on matters of indecision by subjects or parties to a clinical trial, regarding a clinical trial.

c) Providing its opinion to the Ministry to provide basis for clinical trial policies

(2) The Advisory Board for Clinical Trials has the following operating principles and procedures:

a) At its first meeting, the Advisory Board for Clinical Trials elects a deputy chair among its members.

b) Members sitting on the Advisory Board for Clinical Trials have an office term of two years, and any members expiring their term may be reappointed.

c) Any member who fails to attend three consecutive or five nonconsecutive 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.

ç) 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.

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

e) Standard operating procedures of the Advisory Board for Clinical Trials are prepared by the Agency.

f) Secretarial service for the Advisory Board for Clinical Trials is provided by the Agency.

**Observational drug studies**

**ARTICLE 31 –** (1) Observational drug studies may not be conducted without ethics committee approval and Agency's permission. Principles for these studies will be provided in guidelines issued by the Agency.

**Training**

**ARTICLE 32 –** (1) To train and develop principal investigators or investigators, healthcare personnel or other persons engaged in research on good clinical practice, the Agency may hold courses or seminars, or authorize other agencies or institutions desiring to hold such courses or seminars in accordance with guidelines to be issued by the Agency.

**Guideline**

**ARTICLE 33 –** (1) The Agency will issue guidelines to explain and provide guidance on implementation of this Regulation.

## CHAPTER EIGHT
## Miscellaneous and Final Provisions

**Matters not provided herein**

**ARTICLE 34 –** (1) Matters not provided in this Regulation will be governed by the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, the Medical Deontology Regulation put into force by Cabinet of Ministers' Decree #4/12578 of 13.01.1960, the provisions concerning the rights of subjects taking part in a study as provided in the Regulation on Patient Rights, published in the Official Gazette #23420 of 01.08.1998, and other applicable regulatory provisions.

**Repealed regulation**

**ARTICLE 35 –** (1) The Regulation on Clinical Trials, published in Official Gazette #28030 of 19.08.2011 is hereby repealed.

**Transitional Provision**

**PROVISIONAL ARTICLE 2 –** (1) The basic training on good clinical practices and clinical researches of ethics committee members who are healthcare professionals taking part in existing ethics committees formed in compliance with the regulation and approved by the Agency must be completed by 01/04/2016.

**Effectiveness**

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

**Enforcement**

**ARTICLE 37 –** (1) This Regulation will be enforced by the President of Turkish Medicines and Medical Devices Agency.

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