REGULATION

From the Turkish Medicine and Medical Device Agency:

REGULATION ON CLINICAL TRIALS

CHAPTER ONE

Purpose, Scope, Basis and Definitions

Purpose

ARTICLE 1 – (1) This Regulation aims to regulate the procedures and principles for organization, duties, operations of the Clinical Trials Advisory Board and ethics committees and for conducting clinical trials on human volunteers and the protection of volunteers' rights in accordance with the international agreements and conventions to which Turkey is a party and the standards of the European Union and good clinical practices.

Scope

ARTICLE 2 **–** (1) This Regulation covers drug clinical trials, including bioavailability and bioequivalence studies, to be performed on humans with drugs or medical products or herbal medical products, even if they are registered or permitted, as well as non-drug clinical trials, clinical trial facilities and the real persons or legal entities who will conduct these trials.

(2) Retrospective studies are not covered by this Regulation.

Basis

ARTICLE 3 – (1) This Regulation is issued based on additional Article 10 of the Health Services Fundamental Law, dated 7/5/1987, No. 3359; and Articles 27 and 40 of the Statutory Decree on Organization and Functions of the Ministry of Health and Subsidiaries dated 11/10/2011, No. 663; and in parallel with Directives 2001/20/EC and 2005/28/EC on Good Clinical Practices of the legislation of the European Union concerning medicinal products.

Definitions

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

a) Adverse event: Any untoward medical occurrence in a volunteer, whether or not having a causal relationship with the treatment administered,

b) Adverse reaction: Any unwanted and unintended response in a volunteer participating in the clinical trial,

c) Investigator: The person taking part in the trial under supervision of the Principal Investigator,

ç) Investigator's brochure: The documents relating to the clinical and nonclinical data on the investigational product(s) or procedure.

d) Trial protocol: A document that details the objective, design, methodology,

statistical methods to be used and trial-related arrangements,

e) Investigational product: The pharmaceutical form of the placebo or the active substance being tested or used as reference product in the clinical trial,

f) Relative bioavailability: The bioavailability which is obtained by comparing the bioavailability obtained with a pharmaceutical form administered through a route other than intravenous administration with the bioavailability or obtained by the same route but providing higher bioavailability,

g) Ministry: The Ministry of Health,

ğ) Unexpected serious adverse reaction: Any serious adverse reaction with a nature, severity or result not consistent with the reference safety information,

h) Informed consent form: A document which proves in writing that consent is obtained after detailed and clear information about the trial is provided,

ı) Bioequivalence: The similarity of two pharmaceutically equivalent drug products in such a way that their bioavailability and thus their effects are in principle the same in terms of efficacy and safety after their administration in the same molar dosage,

i) Bioavailability: The rate and extent to which the active ingredient or its active moiety is absorbed from a pharmaceutical product and becomes available at the site of action in the body or in the biological fluid that reflects it, in general in the serum or plasma,

j) Serious adverse event or reaction: Any adverse event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect,

k) Multi-center clinical trial: A clinical trial conducted at more than one site according to a single protocol, therefore involving more than one principal investigator,

l) Inspection: Activities of the Institution of inspecting study-related documents and records the quality assurance arrangements and sites that are 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,

m) Sponsor: An individual, institution, or organization responsible for the initiation, conduct and/or funding of a clinical trial,

n) Ethics committee: Independent committees constituted and approved by the Institution to provide scientific and ethical opinion on matters related to the trial protocol, and the methodology and documents to be used for informing volunteers, as well as the consent obtained from these individuals, with a view to protecting the rights, safety and well-being of study volunteers,

o) Volunteer: 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,

ö) Observational drug study: Epidemiological studies to collect data on a spontaneously prescribed drug in patients undergoing treatment in the indications, dosage and administration methods for which the product has been registered in Turkey according to the current diagnostic and therapeutic guidelines of the Ministry described in the Guidelines of Observational Studies on Drugs,

p) Drug or medicinal product for human use: Any natural, synthetically or biotechnologically derived active substance or combination of substances administered to humans with a view to prevent, diagnose or treat a disease, or to correct, regulate or modify a physiological function,

r) Non-drug clinical trial: Any investigation on a new surgical method, trial on stem cell transplantation, or trial on tissue or organ transplantation to be conducted on humans except drug, biological and medicinal products and medical devices and cosmetics,

s) Good clinical practices: 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 international scientific and ethical standards for protecting the rights and physical integrity of volunteers, ensuring reliability of study data and protecting confidentiality,

ş) Vulnerable: Any person who meets the criteria of disability as described in the Turkish Civil Code #4721 of 22/11/2001,

t) Clinical trial: Any investigation in human volunteers intended to discover or approve the clinical, pharmacological and/or other pharmacodynamic effects of investigational product(s), to identify any adverse events or reactions to investigational product(s), to study absorption, distribution, metabolism and excretion of the investigational product(s) and to research their safety and/or efficacy,

u) Advisory Board for Clinical Trials: A board that will be established to provide opinion to the Ministry on matters related to clinical trials,

Ü) Institution: Turkish Medicine and Medical Device Agency,

v) Absolute bioavailability: Bioavailability as compared to the bioavailability measured by intravenous administration of the same molar dosage of a drug,

y) Principal investigator: A physician or dentist who has completed specialty education or doctorate education in the branch relating to the trial scope and who is responsible for the conduct of the trial,

z) Contract Research Organization: An independent organization operating according to good clinical practices principles, to which the sponsor has delegated all or some of its duties and authorizations in connection with the clinical trial by a written contract.

SECTION TWO

General Principles of the Trial and Obtaining Consent for the Trial

General Principles of the Trial

ARTICLE 5 – (1) The following are required for conducting a trial on volunteers:

a) The trial must first be conducted in a study in a non-human in vitro environment or in a sufficient number of animals.

b) 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 as well.

c) The scientific benefits and public interest expected from a trial cannot prevail over the health of the volunteers involved in the trial, or over any potential risks to their health or other personal rights.

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

d) 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.

e) The trial shall not involve any procedures that inflict pain on the volunteer to a degree that would be incompatible with human dignity.

f) The trial shall be designed in a manner to minimize pain, discomfort, fear, and any risks related to the patient's disease or stage of development. Both risk limit and degree of discomfort must be particularly defined and controlled on a regular basis.

g) The purpose of the trial must outweigh the difficulty experienced by and the health hazard to the person.

ğ) The study shall not have any predictable harmful and permanent effects on human health.

h) A trial may be initiated if it is concluded by the relevant Ethics Committee that the expected benefits of a trial outweigh the potential risks, with due regard for personal rights and that informed consent forms of the volunteers are duly obtained after relevant ethics committee approval and permission of the Institution are obtained. The trial may only be conducted for as long as these conditions are continuously met.

ı) Prior to participation in the trial, the volunteer or the volunteer's legal representative shall be informed by a principal investigator from the trial team or a physician or dentist who is competent on the subject matter of the trial sufficiently and in a manner comprehensible to the volunteer or the volunteer's legal representative on the purpose, methodology, expected benefits, predictable 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.

i) Volunteer's consent which is not dependent on any provision of personal gain 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 Volunteer Informed Consent Form including the

information described in paragraph (ı) above.

j) At least one person from the trial team will be appointed as a contact person for the volunteer to receive information at any time on his or her health or on the progress of the trial.

k) A volunteer may withdraw from the trial at their own discretion, with or without giving a reason, at any time he/she wishes, and may not be deprived of any of his/her rights during subsequent medical follow up and treatment based on such decisions.

l) In order to cover volunteers against harm(s) which may arise out of the clinical trial, insurance must be provided to volunteers who take part in clinical trials as per requirements of the legislation, except Phase IV clinical trials mentioned in Article 10, paragraph one, subparagraph (ç) and observational drug studies. However, this condition is determined according to the nature of the trial in non-drug clinical trials.

m) Except insurance coverage, no persuasive incentive or financial benefit shall be offered to a volunteer or his/her legal representative 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.

n) A volunteer's identification details will not be disclosed in case results of a clinical trial are published.

Participation of children in a clinical trial

ARTICLE 6 – (1) Where the subject matter of a 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 the data obtained as a result of the trials conducted on adults also on children, it may be permitted to conduct a clinical trial on children within the framework of the below conditions and the considerations highlighted above in Article 5, provided that the clinical trial carries no foreseeable serious risk to volunteers' well-being and that there is a general medical opinion that the clinical trial will directly benefit the volunteers:

a) There must be a general medical opinion that the product or implementation which is to be studied in the trial has no known risk on children.

b) If the child is capable of declaring his/her consent, in addition to his/her written consent, the written consent of his/her mother and father or guardian if he/she is under guardianship shall be obtained after informing in accordance with Article 5, paragraph one and subparagraph (l).

c) Where the child refuses to participate in the trial or wants to withdraw from the trial at any phase thereof, he/she shall be removed from the trial.

ç) If the child is capable of assessing the information provided to him or her and reaching a conclusion on the matter, all information relevant to the clinical trial will be communicated to him/her in an appropriate manner.

d) The ethics committee will be informed on the clinical, ethical, psychological and social issues associated with the clinical trial by a pediatrician, or, in the case of a clinical trial in children related to dentistry, by a dentist who holds a doctorate or

specialty degree in pediatric dentistry and the protocol will be assessed accordingly.

e) 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 pediatrician, or, in the case of a clinical trial in children related to pediatric dentistry, by a dentist who holds a doctorate or medical specialty degree in pediatric dentistry.

f) 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 7 – (1) Where the subject matter 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 risk to the health of the volunteer and baby or fetus, and that there is a general medical opinion that the clinical trial will directly benefit the volunteers:

a) 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.

b) The written consent of pregnant, postpartum or breastfeeding women is obtained after informing them in the manner described in Article 5, paragraph one and subparagraph (ı).

c) Where a pregnant, postpartum or breastfeeding woman refuses to participate in the trial or wants to withdraw from the trial at any phase thereof, she shall be removed from the trial.

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 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 8 – (1) Where the subject of a 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 on 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 that there is a general medical opinion that the clinical trial will directly benefit the

vulnerable:

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

b) If the vulnerable individual is capable of declaring his/her consent, written consent of the vulnerable individual and his/her guardian is obtained after providing information in accordance with Article 5, paragraph one and subparagraph (ı).

c) If the vulnerable individual is capable of assessing the information provided to him or her and reaching a conclusion on the matter, in case the vulnerable individual refuses to participate in the trial or wants to withdraw from the trial at any phase thereof, he/she shall be removed from the trial immediately.

ç) The ethics committee 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 purpose of the study, and the protocol shall be assessed accordingly.

d) No persuasive incentive or financial benefit may be offered in connection with a clinical trial in vulnerable individuals, other than the covering of necessary expenses arising from their participation in the clinical trial.

Participation in a clinical trial by individuals who are in intensive care and unconscious

ARTICLE 9 – (1) Where the subject matter of a clinical trial is directly related to individuals who are in intensive care and unconscious or is a condition that can be investigated only in individuals who are in intensive care and unconscious or available treatment options of individuals who are in intensive care and unconscious have been completely exhausted, it may be permitted to conduct a clinical trial in individuals who are in intensive care and unconscious within the framework of the below conditions and together with the considerations highlighted above in Article 5, provided that the clinical trial carries no foreseeable risk to the health of the individuals who are in intensive care and unconscious and that there is a general medical opinion that the clinical trial will directly benefit the individuals who are in intensive care and unconscious:

a) There must be a general medical opinion that the product or implementation which is to be studied in the trial has no known risk on the individuals who are in intensive care and unconscious.

b) Legal representatives, if any, or relatives if there is no legal representative, of the individuals who are in intensive care and unconscious are informed and their written consent is obtained in accordance with Article 5, paragraph one and subparagraph (l).

c) If the individuals who are in intensive care and unconscious become capable of assessing the information provided to them and reach a conclusion on the matter, in case the individuals who are in intensive care and unconscious refuse to participate in the trial or want to withdraw from the trial at any phase thereof, they shall be removed from the trial immediately.

ç) The ethics committee will be informed on the clinical, ethical, psychological

and social issues associated with the clinical trial by a physician who has a specialty degree in the field which is the subject matter of the trial and the protocol will be assessed accordingly.

d) No persuasive incentive or financial benefit may be offered in connection with a clinical trial in the individuals who are in intensive care and unconscious, other than the covering of necessary expenses arising from their participation in the clinical trial.

(2) In case legal representatives or relatives of individuals who are in intensive care and unconscious can not be reached and thus their consent can not be obtained, provided that the following conditions are satisfied together with the provisions of the first paragraph, individuals who are in intensive care and unconscious may be included in the trial under the responsibility of a principal investigator or physician:

a) The ethics committee evaluates in advance if the proposed trial protocol or other documents satisfy the ethical issues sufficiently in the said trial,

b) There is a general medical opinion that the clinical trial will directly benefit the individuals who are in intensive care and unconscious in conditions which develop suddenly and require a physician's response right away such as cardiac arrest, head trauma, central nervous system infections, internal bleeding of the brain and where available treatment options are completely exhausted.

CHAPTER THREE

Principles for Conducting Trials

Periods 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 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. Phase I or Period I clinical trials shall not begin before pre-clinical pharmacological, toxicological and similar research for a newly developed investigational product is performed fully and by implementing adequate 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 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 of patients where products registered in Turkey are further investigated in

terms of their approved indications dosage and administration methods, 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 sites which are preferably designed for clinical trials at centers for health practice and research established within universities, including Gulhane Military Medical Academy and military training and research hospitals, approved centers for research and development which are part of universities, and the Ministry's training and research hospitals which are suitable for and possess appropriate staff, equipment and laboratory means to ensure the safety of research volunteers and proper conduct and monitoring of a clinical trial and appropriate emergency care should it be necessary.

(2) Phase I clinical trials and bioavailability–bioequivalence studies are conducted at health organizations and institutions and research and development centers within the Ministry and universities which are approved by the Institution and which have the facilities for emergency treatment and which satisfy the respective standards defined for each of them.

(3) Sites where clinical trials will be conducted on the basis of the Guidelines for Good Clinical Practices must minimally have:

a) The necessary staff and equipment at an adequate level which is appropriate for 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 for volunteers, including cases requiring emergency care,

ç) The sufficient means and equipment to enable the transfer of 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 after the study is completed.

Clinical Trial application and authorization

ARTICLE 12 – (1) Concurrent applications may be made to the ethics committee and the Institution in order to obtain authorization for clinical trials which are within the scope of this Regulation.

(2) The application dossier for a trial shall be prepared according to the Guidelines for Good Clinical Practices and other applicable guidelines, using the application form and its relevant annexes on the Institution's website.

(3) The decision of one ethics committee shall be sufficient for multi-center clinical trials.

(4) The application for a clinical trial will be made to the relevant ethics committee and the Institution by the sponsor, consisting of real persons or legal entities, 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) Provided that the application is duly made, the information and documents required in the application are provided completely, and the decision of the ethics committee is presented, the Institution shall review and conclude an application within thirty days.

(6) If the Institution adopts an unfavorable decision regarding the request for conducting the clinical trial, this decision will be notified to the sponsor together with the justification of the decision. The sponsor shall be entitled to resubmit the application after making the required amendments to address the issues raised in the decision, or to file a reasoned objection against the decision within fifteen days. At this time the review process will be frozen, if the requested changes are not fulfilled or an acceptable justification cannot be offered, the Institution may reject the clinical trial.

(7) In trials where products containing genetically modified organisms or products involving cellular treatments or gene therapy and in non-drug clinical trials, a period of thirty days shall be added to the period specified for authorization of the Institution.

Commencement and conduct of clinical trials

ARTICLE 13 – (1) Clinical trials which require authorization of the Institution shall not begin without permission of the Institution.

(2) Of the changes which occur during performance of the trial, those which qualify as notification and those which require decision and permission shall be determined by the Guidelines for Good Clinical Practices. The changes which require decision and permission shall be reviewed and concluded within fifteen days by the ethics committee and within thirty days by the Institution following submission of the decision of the ethics committee.

(3) Clinical trials shall be conducted in the following manner:

a) Clinical trials falling within the scope of this Regulation shall be conducted by a team suitable for the nature of the study, led by a principal investigator. Phase I clinical trials and bioavailability-bioequivalence studies are conducted by an appropriate team that has adequate training and experience in good clinical practices and a pharmacologist physician who has completed specialty education or a doctorate degree.

b) On condition that provisions in the second paragraph are reserved, the sponsor or the principal investigator or an investigator who is a physician or dentist will take any urgent safety precautions necessary to protect 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 have an impact on volunteers' safety. The principal investigator or the sponsor will notify the relevant ethics committee or the Institution on these new circumstances and the precautions taken. Otherwise, the Institution shall suspend the study.

c) If a clinical trial, although permitted by the Institution, can not be commenced on the date specified in the application dossier the reasons underlying

such delay will be notified to the Institution within ninety days.

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 this 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 practices provided that a written contract is executed and information is given to the Institution. Delegation of duties to a contract research organization shall not release the sponsor's potential legal and penal liability in connection with such delegated duties. The sponsor and the contract research organization shall have joint responsibility for the outcome of the works and operations which are the subject matter of the contract.

Suspension or termination of clinical trials

ARTICLE 14 – (1) The Institution 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 the trial. If these conditions are seen as not possible to be met, or it is concluded that they can not be met within the prescribed timeframe, or if the safety of the volunteers will be compromised in the meantime, the clinical trial will be directly suspended.

(2) Where there is no direct risk posed to volunteers, the sponsor or principal investigator may be requested to submit their view on the issue. In that case, the sponsor or the principal investigator shall submit his/her opinion regarding the issue to the Institution within fifteen days.

(3) If a trial is stopped by the sponsor without being completed after it has commenced, the decision for stopping and the justifications thereof shall be notified to the Institution and the relevant ethics committee within fifteen days together with an information letter describing the measures taken for continuation of treatment of the volunteers admitted to the study.

(4) The sponsor shall notify completion of a trial to the Institution and ethics committee within ninety days following termination date.

(5) A suspension or termination decision regarding the clinical trial and the justification thereof shall be notified to the ethics committee, sponsor and 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 or caused to be maintained.

(2) The responsibility rests with the principal investigator at each center for receiving delivery and preservation of investigational products, dispensing the investigational products according to written request or the study protocol, controlling the inventory, and performing the procedures for any remaining investigational products and keeping the records. The principal investigator shall appoint a pharmacist for performance of these procedures.

Manufacture, importation, and labeling of investigational products

ARTICLE 16 – (1) It shall be guaranteed that the investigational products are manufactured in accordance with the rules in the Guidelines for Good Manufacturing Practices.

(2) Permission of the Institution shall be obtained for manufacturing or import of the products which will be used in the trial.

(3) Sponsors that will manufacture or import an investigational product must meet the following requirements:

a) The application made to the Institution 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 practices 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 no less than fourteen years.

(4) The investigational product shall be labeled in Turkish on the outer packaging, or if it has no outer packaging, on the outermost packaging, in accordance with the Guidelines for Good Manufacturing Practices.

Recall 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 physician or dentist shall be immediately recalled from locations where these were dispensed and notified to the Institution within fifteen days with supporting documentation as a report.

(2) The recall of investigational products and the particulars of the process and precautions to be taken with respect to the recalled investigational products will be detailed in the report submitted to the Institution.

CHAPTER FIVE

Reporting of Adverse Events and Serious Adverse Reactions

Other Notifications, Supervision and Responsibility

Reporting of adverse events

ARTICLE 18 – (1) The principal investigator or an investigator assigned by the former shall immediately report all adverse events mentioned in the protocol or the investigator’s brochure, except those which do not need to be reported, to the sponsor. A single code number shall be used for study volunteers in the emergency

report and subsequent reports.

(2) Adverse events or laboratory findings identified as critical to safety evaluations shall be immediately reported to the sponsor in the manner and the period stated in the protocol.

(3) In the event of the death of a volunteer, the principal investigator or an investigator assigned by the former shall provide the sponsor, the ethics committee, and the Institution with any additional information.

(4) The sponsor shall keep detailed records of all adverse events reported to them by the principal investigator or investigator. These records shall be submitted to the Institution and the ethics committee upon request.

Reporting of serious adverse reactions

ARTICLE 19 – (1) The sponsor shall ensure that all relevant information about serious adverse reactions that occur during the trial are reported to the ethics committee and the Institution within no more than seven days after receiving such information. Relevant follow-up reports containing additional information on the cases shall be subsequently communicated to the ethics committee and Institution within eight days after receiving such information.

(2) All other unexpected serious adverse reactions shall be reported by the sponsor to the ethics committee and the Institution no later than fifteen days after having first knowledge of this information.

(3) The sponsor shall also inform all investigators and the principal investigator.

(4) Once a year, the sponsor shall provide the ethics committee and the Institution with a listing of all the observed suspected serious adverse reactions, including information relevant to volunteers' safety, using the interim report form provided in the relevant guidelines to be issued by the Institution. In short-term studies or where necessary, the Institution may also require submission of reports in shorter times.

Other notifications

ARTICLE 20 – (1) In multi-center clinical trials, the interim report and the final report prepared using a template of the forms provided in the relevant guidelines and internet site of the Institution shall include the relevant results from all centers taking part in the trial.

(2) Of the trial related assignments, those which qualify as notification and those which require decision and permission shall be determined by the Guidelines for Good Clinical Practices. However, the Institution shall be entitled to cancel those which qualify as notification, providing the justification thereof.

(3) The responsibility to ensure regular submission of notifications to the Institution rests with the sponsor.

Trial records, confidentiality and transfer

ARTICLE 21 – (1) All records related to the trial shall be regularly kept by the sponsor and principal investigator or investigator, and maintained for no less than

fourteen years after the trial is completed at all centers.

(2) The ethics committee and the Institution must be notified in the event that the trial is transferred by the sponsor for any reason. The Institution shall approve the transfer if it deems fit. Where the trial is transferred, the new owner of the data and documents shall be responsible for maintaining and archiving the same.

(3) Information and documents related with the trial shall be archived in accordance with the provisions of the relevant guidelines.

(4) Confidentiality of documents related to a trial is essential. These documents shall be disclosed to authorized parties only upon the request of legally authorized persons or bodies.

Inspection

ARTICLE 22 – (1) The Institution shall inspect with or without prior notice the trials conducted in Turkey or abroad, the trial sites, the sponsor and the contract research organization, the sites where the investigational products are manufactured, the laboratories where the analyses relating to the trial are conducted, ethics committees in terms of their compliance with the provisions of this Regulation and other relevant legislation.

(2) Inspectors shall 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 practices.

(3) Inspectors of good clinical practices shall be 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 dedicated for using the products, and the costs of all examinations, tests, analyses and treatments used in the trial shall be covered by the sponsor. Volunteers or social security institutions shall not be required to pay such costs.

(2) Real persons or legal entities that shall conduct a clinical trial must detail the particulars of trial funding in the application dossier.

(3) The fact that a Volunteer Informed Consent Form has been obtained from volunteers participating in a clinical trial shall not eliminate such volunteer's entitlement to seek compensation of damages experienced by him/her in connection with the trial.

»**Prohibitions**

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ARTICLE 24 – (1) Trials which are within the scope of this Regulation shall not be conducted in violation of the procedures and principles set forth in this Regulation or other relevant legislation.

Administrative sanctions

ARTICLE 25 – (1) If the terms related to clinical trials are violated, the related

trial, or for international multi-national clinical trials the part of the trial performed in Turkey, may be suspended or terminated by the Institution. Upon elimination of the causes of suspension, the case will be notified by the sponsor to the Institution and the trial shall resume if considered appropriate by the Institution.

(2) The Institution will warn ethics committees which fail to operate in compliance with ethical rules, or fail to satisfy the principles of Ethics Committee Standard Operation Methods published by the Institution, or are found to have deficiencies as the result of inspection, in terms of the place, secretariat, archives and other equipment which are required for conducting the works. The Institution shall withdraw its approval given under Article 26, second paragraph hereof and membership of the chairman of the ethics committee shall be suspended for two years if the cause of the warning is not eliminated within the specified period of time.

(3) Turkish Penal Code No. 5237 dated 26/9/2004 and the provisions of other legislation shall apply depending on the nature of the deeds, on those who act and conduct activities in violation of the provisions indicated in this Regulation.

CHAPTER SIX

Structure, Operating Procedures and Principles, and Duties of Ethics Committees

Structure of Ethics Committees

ARTICLE 26 – (1) Ethics committees, comprised of not less than seven and not more than fifteen members whose majority are healthcare professionals holding doctorate degrees or medical specialty degrees, are established in order to make scientific and ethical evaluations on the methods and documents to be used for informing volunteers and the consent to be given by such people in addition to other trial related matters with a view to protect the rights, safety and well-being of volunteers.

(2) Ethics committees are established by approval of the Institution following proposals for establishment of such committees by university presidents, the general secretary and dean in universities, Public Hospital Associations and Gulhane Military Medical Academy respectively.

(3) Ethics committees shall be formed as a Clinical Trials Ethics Committee and Bioavailability–Bioequivalence Ethics Committee.

(4) The Clinical Trials Ethics Committee shall be formed in order to perform scientific and ethical evaluation on all trials except bioavailability–bioequivalence studies.

(5) The Bioavailability–Bioequivalence Ethics Committee shall be formed in order to perform scientific and ethical evaluation on bioavailability–bioequivalence studies.

(6) A minimum of three members of the ethics committee must be from outside the institution where the ethics committee secretariat is located.

(7) A member of an ethics committee shall not serve as a member in more than one ethics committee.

(8) Top managers of the site where clinical investigation is conducted shall not

serve in ethics committees.

(9) Ethics committees shall engage in direct written communication via their own secretariat with the Institution following their approval by the Institution.

(10) A Clinical Trials Ethics Committee shall consist of members who have the following qualifications at a minimum:

a) Specialist physicians who have preferably served as investigators in international clinical trials conducted in accordance with the rules of good clinical practices and who are preferably selected from different specialty fields in medicine,

b) A pharmacist holding a doctorate in pharmacology or physician holding a doctorate or specialty degree in pharmacology,

c) A person holding a doctorate degree in biostatistics or a physician holding a doctorate or specialty degree in public health,

ç) An engineer or specialist who works in the biomedical field; if not available, a biophysicist or physiologist,

d) Lawyer,

e) Non healthcare professional,

f) A person holding a doctorate or specialty degree in medical ethics or deontology, if any,

g) Clinical pharmacist, if any.

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

a) Specialist physicians who have preferably served as investigators in international clinical trials conducted in accordance with the rules of good clinical practices,

b) A pharmacist holding a doctorate in pharmacology or physician holding a doctorate or specialty degree in pharmacology,

c) A person holding a doctorate degree in biostatistics or a physician holding a doctorate or specialty degree in public health,

ç) A pharmacist who preferably has obtained a doctorate degree in biopharmaceutical, pharmacokinetics or pharmaceutical technology,

d) A pharmacist who preferably holds a doctorate degree in pharmaceutical chemistry or analytical chemistry, or a chemist or chemical engineer holding a doctorate degree in the aforesaid fields,

e) Lawyer,

f) Non healthcare professional

g) A person holding a doctorate or specialty degree in medical ethics or deontology, if any.

Operating procedures and principles of ethics committees

ARTICLE 27 – (1) The operating procedures and principles of ethics committees are the following:

a) Ethics committees are independent in assessing and approving clinical trial applications in terms of scientific and ethical considerations.

b) Ethics committee members are obligated to comply with the confidentiality requirement for all information that has been made available to them.

c) Ethics committee members will take office upon signing a confidentiality agreement and a letter of commitment which will be drawn up by the Institution.

ç) An ethics committee member who is affiliated with the trial under review or has a function in the trial may not take part in ethics committee discussions and in the voting on this trial and may not sign the committee decision.

d) Ethics committee members will convene with a two-thirds majority of the total number of members, and resolves with an absolute majority of the full number of members.

e) Ethics committee members' term of office is two years, and members whose terms expire may be reappointed.

f) Any members who fail to attend three consecutive or five non-consecutive meetings without any excuse throughout his/her membership term shall be automatically removed from membership. A member having the same qualifications shall be appointed in place of the member whose term has expired or who is removed from membership.

g) Where necessary, ethics committees may obtain the written opinion of specialists on the related area or on a complementary area and may invite such specialists to meetings to function as consultants.

ğ) Operation methods of ethics committees shall be determined by and posted on the internet site of the Institution. Ethics committees conduct their activities in accordance with such specified standards.

Duties and powers of ethics committees

ARTICLE 28 – (1) The duties and powers of the ethics committees are as follows:

a) The clinical trial applications made within the scope of this Regulation shall be evaluated by ethics committees which are established according to Article 26.

b) Other institutions or organizations shall not establish an ethics committee or any other board or agency which will perform the functions of an ethics committee for evaluation of the matters which are within the scope of this Regulation.

c) While the Ethics Committee forms an opinion on the trial application, it shall at a minimum evaluate:

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) For trials to be performed for the first time on humans, the obligation that the trial must first be performed in a non-human in vitro environment and on a sufficient number of animals,

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

5) Trial protocol,

6) An evaluation of the contents of the investigator's brochure and whether it has been prepared in due form,

7) The documented information submitted relating to the study, the method used for obtaining the consent of volunteers, and adequacy of the justification for conducting the study in vulnerable individuals, children, pregnant, postpartum or breastfeeding women or individuals who are in intensive care and unconscious,

8) Responsibility of the principal investigator, or investigator, or the sponsor in the event of injury or death, including permanent health problems potentially resulting from the trial,

9) Payment of compensation for trial-related injury or death,

10) Regulations regarding admitting volunteers to the trial,

11) Qualifications of the trial team in comparison to the nature of the trial,

ç) The Ethics Committee may monitor the approved applications during the trial and at the site.

d) The Clinical Trials Ethics Committee shall communicate its opinion to the applicant no later than fifteen days following the respective application date, whereas the Bioavailability–Bioequivalence Studies Ethics Committee shall communicate its opinion to the applicant no later than seven days following the respective application date.

e) For trials bearing genetically modified organisms and trials to be carried out using cellular treatments or products containing gene treatment or non-drug clinical trials, a further thirty days may be added to the fifteen-day time specified for obtaining the approval of the ethics committee.

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 suspended until the required data and documents are submitted to the ethics committee.

PART SEVEN

Structure, Operating Procedures and Principles, and Duties of Ethics Committees

Observational Drug Studies and Training

Structure of Clinical Trials Advisory Board

ARTICLE 29 – (1) The Clinical Trials Advisory Board shall be chaired by the Undersecretary of the Ministry of Health or a Deputy Undersecretary who is deemed fit for this role by the former and shall consist of three individuals appointed by the Institution who hold a specialty degree or doctorate degree in surgical, internal and basic sciences of medicine, a clinical psychologist and a theologian, 1st Degree Legal Consultant of the Institution or a legal consultant appointed by the former.

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

ARTICLE 30 – (1) The Clinical Trials Advisory Board shall provide its opinion on clinical trial related matters which require expert opinion forwarded by ethics committees or parties to the relevant clinical trial to the Institution.

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

a) The Clinical Trials Advisory Board will select a deputy chairman from amongst its members in its first meeting.

b) The term of office of members appointed to the Clinical Trials Advisory Board is two years and members whose terms of office are terminated may be reelected.

c) Any member who fails to attend three consecutive or five non-consecutive meetings without any excuse 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 Clinical Trials Advisory Board convenes with a two-thirds majority of the full number of members and resolves with an absolute majority of the full number of members.

d) If required, the Board may request the opinion of related specialists or may invite these specialists to hear their opinions.

e) The Standard Operating Method of the Clinical Trials Advisory Board shall be determined by the Institution.

f) Secretarial works of the Clinical Trials Advisory Board will be carried out by the Institution.

Observational drug studies

ARTICLE 31 – (1) Observational drug studies shall not be conducted without the approval of the ethics committee and permission of the Institution. The principles regarding such studies are specified in the guidelines to be published by the Institution.

Training

ARTICLE 32 – (1) The Institution shall be entitled to organize courses or seminars for the purpose of training qualified investigators and healthcare staff in the field of good clinical practices or shall be entitled to approve the organization of such courses and seminars by other institutions and entities in accordance with the

guidelines to be published by the Institution.

Guidelines

ARTICLE 33 – (1) The Institution shall publish an instructional and descriptive guide for the application of this Regulation.

PART EIGHT

Miscellaneous and Final Provisions

Absence of Provisions

ARTICLE 34 – (1) For any matter not contained in this Regulation, the Contract for Protection of Human Rights and Human Dignity for Biological and Medical Practice, Medical Deontology Regulation effected under Council of Ministers Decree no. 4/12578 dated 13/1/1960, Patient Rights Regulation published in the Official Gazette No. 23420 dated 1/8/1998 with respect to the rights of volunteers participating in trials and the provisions of other legislation shall apply.

Abolished regulation

ARTICLE 35 – (1) The Regulation on Clinical Trials published in the Official Gazette dated 19/08/2011 No. 28030 has been abolished.

Existing Ethics Committees

PROVISIONAL ARTICLE 1 – (1) The ethics committees which have been approved as per the Regulation on Clinical Trials published in the Official Gazette dated 19/08/2011 No. 28030 may continue their functions for no more than six months following publication of this Regulation.

Effect

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

Enforcement

ARTICLE 37 – (1) The provisions of this Regulation will be enforced by the President of the Turkish Medicine and Medical Device Agency.