REGULATION

Issued by Turkish Medicines and Medical Devices Agency:

A REGULATION TO AMEND THE REGULATION ON CLINICAL TRIALS

ARTICLE 1 – The Regulation on Clinical Trials, published in Official Gazette #28617 dated 13.04.2013, is hereby renamed as follows:

"Regulation on Clinical Trials of Medicinal and Biological Products."

ARTICLE 2 – In the same Regulation, the first paragraph of Article 2 is hereby revised as follows:

"(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."

ARTICLE 3 – In the same Regulation, subparagraph (r) of the first paragraph of Article 4 is hereby repealed, and subparagraphs (aa), (bb) and (cc) are appended thereto as follows, respectively:

"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."

ARTICLE 4 – In the same Regulation, subparagraph (l) of the first paragraph of Article 5 is hereby revised as follows:

"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."

ARTICLE 5 – In the same Regulation, subparagraphs (d) and (e) of the first paragraph of

Article 6 are hereby revised as follows, respectively:

"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."

ARTICLE 6 – In the same Regulation, the first paragraph of Article 11 is hereby appended with the following sentence, and the third paragraph with a subparagraph (e) as follows:

"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."

"(e) a certificate of authorization issued by the Agency."

ARTICLE 7 – In the same Regulation, the seventh paragraph of Article 12 is hereby revised as follows:

"(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."

ARTICLE 8 – In the same Regulation, the first paragraph of Article 13 is hereby appended with the following sentence:

"These studies will be entered in a public register, respecting the privacy of personal information."

ARTICLE 9 – In the same Regulation, the last sentence of the second paragraph of Article 15 is hereby revised as follows:

"The principal investigator may appoint, preferably, a pharmacist to perform these functions."

ARTICLE 10 – In the same Regulation, the words "fourteen years," appearing in subparagraph (b) of the third paragraph of Article 16, are hereby replaced with "five years."

ARTICLE 11 – In the same Regulation, the first and second paragraphs of Article 18 are hereby revised as follows, respectively:

"(1) The principal investigator, or an investigator appointed by the principal investigator, will immediately report all adverse events to the sponsor, except those specified in the protocol or the investigator's brochure and those deemed not requiring immediate reporting. This urgent

report will be followed by a detailed report. A single subject identifier will be used in the urgent report and any subsequent ones."

(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."

ARTICLE 12 – In the same Regulation, Article 19 is hereby revised as follows:

"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."

ARTICLE 13 – In the same Regulation, the words "fourteen years," appearing in the first paragraph of Article 21 are hereby replaced with "five years."

ARTICLE 14 – In the same Regulation, the second paragraph of Article 22 is hereby revised as follows:

"(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."

ARTICLE 15 – In the same Regulation, the first paragraph of Article 23 is hereby revised as follows:

"(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."

ARTICLE 16 – In the same Regulation, the ninth paragraph of Article 26, and subparagraph (g) of the tenth paragraph thereof are hereby repealed, and the first paragraph and subparagraph (b) of the tenth paragraph, and subparagraphs (b) and (ç) of the eleventh paragraph

are revised as follows:

"(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."

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

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

ARTICLE 17 – In the same Regulation, subparagraph (f) of the first paragraph of Article 27 is hereby revised as follows:

"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."

ARTICLE 18 – In the same Regulation, the first paragraph of Article 30 is hereby revised as follows:

"(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."

ARTICLE 19 – In the same Regulation, the words "and clinical trials" are hereby appended after the words "good clinical practice," appearing in the first sentence of the first paragraph of Article 32.

ARTICLE 20 – In the same Regulation, the Transitional Article 1 is hereby repealed, and the following transitional article appended:

Transitional Provision

TRANSITIONAL ARTICLE 2 – (1) Basic training in good clinical practice and clinical trials, of healthcare professionals currently sitting as a member on existing ethics committees that were established according to the Regulation on Clinical Trials, published in Official Gazette #28617 dated 13.04.2013 and approved by Turkish Medicines and Medical Devices Agency, will be completed within not more than nine months from the publication date of this

Regulation.

(2) The authorization certificate to be issued by the Agency must be obtained within not more than two years from the publication date of this Regulation.

ARTICLE 21 – This Regulation will enter into force on the date it is published.

ARTICLE 22 – This Regulation will be enforced by the President of Turkish Medicines and Medical Devices Agency.

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