

GUIDELINE ON THE IMPORTATION OF INVESTIGATIONAL PRODUCTS TO BE USED IN CLINICAL TRIALS

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1. PURPOSE This guideline has been prepared for the purpose of establishing the procedures and principles regarding the importation of investigational products to be used in clinical trials conducted in our country. 2. SCOPE It covers the importation of investigational products to be used in clinical trials whose conduct has been authorized by the Department of Clinical Trials of the Turkish Medicines and Medical Devices Agency. 3. LEGAL BASIS This guideline has been prepared on the basis of subparagraphs (a) and (c) of the first paragraph of Article 508 of the Presidential Decree No. 4 on the Organization of Authorities Affiliated with, Related to or Associated with Ministries and Other Institutions and Organizations dated 15/7/2018; subparagraph (a) of the first paragraph of Article 9 of the Regulation on the Duties and Working Procedures and Principles of the Service Units of the Affiliated Organizations of the Ministry of Health, published in the Official Gazette No. 30278 dated 22/12/2017, and the second paragraph of Article 16 of the Regulation on Clinical Trials of Medicinal Products and Biological Products, published in the Official Gazette No. 28617 dated 13/4/2013. 4. DEFINITIONS 4.1. As used in this guideline; 4.1.1. Investigational Product: the pharmaceutical form of the active substance or placebo tested in a clinical trial or used as reference, 4.1.2. Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), 4.1.3. Proforma Invoice: refers to an invoice, for informational purposes and used in importation procedures, containing information such as the type, quantity and estimated price of the investigational product. 4.2. The definitions specified in the Guideline on Good Clinical Practice and in the relevant legislation shall apply. 5. FUNDAMENTAL PRINCIPLES 5.1. The importation application shall be made, in compliance with the relevant legislation, by the sponsor or its legal representative. 5.2. If the applicant is not the sponsor of the trial; the original authorization document indicating that the legal representative who will carry out the importation process has been authorized by the sponsor for this matter must be submitted as an annex to the conformity application or to the first importation application. In repeated importation applications, the date and number of the application to which the original document was submitted must be specified in the cover letter. 5.3. Applications may be made for the importation of investigational products to be used in clinical trials whose conduct in our country has been authorized by the Department of Clinical Trials. 5.4. Importation applications concerning medical devices that are the subject of the trial must be made to the relevant Department of the Agency. 5.5. For the importation of investigational products subject to control, permission must also be obtained from the relevant Department of our Agency. 5.6. Importation applications may be made after the trial has been authorized by the Department of Clinical Trials. 5.7. Investigational products imported under the scope of this guideline may be used only at approved sites and only for participants included in the trial within the scope of the protocol. 5.8. By signing the relevant application form, the applicant undertakes that the information presented in the application form regarding the investigational product is accurate.

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5.9. Records relating to the importation, distribution, storage, safekeeping at trial sites, consumption and destruction of investigational products must be retained by the sponsor or its legal representative for the period required by the relevant legislation, for submission upon request by the Agency. 5.10. The sponsor is responsible for the distribution of the investigational product, and the investigator responsible for its safekeeping at the trial sites. 6. STORAGE OF

INVESTIGATIONAL PRODUCTS 6.1. Following the completion of the importation, investigational products may be sent directly to the trial sites or may be stored in warehouses holding a permit for storage and distribution services for investigational products used in clinical trials approved by the Agency or holding a manufacturing site permit. 7. PROFORMA INVOICE 7.1. The proforma invoice date, proforma invoice number, name of the manufacturing company, name of the investigational product, packaging form and package content must be specified on proforma invoices. 7.2. Two copies of the proforma invoice bearing a wet/electronic signature must be included as annexes to the application. 7.3. Only the investigational products to be used in the trial, products required solely for the use and distribution of the investigational products, and rescue therapy may be listed on the proforma invoice. 8. IMPORTATION PERMIT APPLICATION 8.1. The application to the Agency shall be made using the cover letter template and application form published on the Agency's website. 8.2. All sections of the application form must be completed in full. The information contained in the application form must be consistent with the protocol approved by the Agency and with the other information and documents. In the event of any changes to this information/documents, an application/notification must be made to the relevant ethics committee and to the Agency for the change in question before making the importation application, and permission must be obtained if required. 8.3. The quantity of investigational product needed for the study must be calculated in the relevant section of the application form. The calculations must be clearly shown in accordance with the maximum dose and maximum treatment duration specified in the protocol, taking into account, where applicable, criteria such as the participants' weight and body mass index, using data such as the quantity of investigational product a participant will receive at one visit, the package content, the number of visits, the interval between visits, etc. 8.4. When making the calculations, the necessary explanations regarding the design of the trial (treatment arms in the study, double-blind, open-label, etc.) must be provided in accordance with the protocol. 8.5. The importation permit application may be made for the quantities of investigational product to be used during a period covering a maximum of one year of the trial and for the safety margins specified in Article 8.6. 8.6. The safety margin shall be determined in the manners specified below; 8.6.1. Where the investigational products are stored in a warehouse, in addition to the quantity of investigational product needed during a period covering one year of the trial, 25% of this quantity may be determined as the safety margin. 8.6.2. In cases where the investigational product is delivered directly to the trial sites and no transfer of the investigational product will be made between the sites, provided that this is undertaken, 25% of the investigational product needed during a period covering one year of the trial

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and the quantity of investigational product sufficient for one volunteer at each trial site for a one-year period may be determined as a safety margin. 8.6.3. In exceptional cases, the safety margin may be increased, provided that the necessary explanations are made in the application form and deemed appropriate by the Agency. 8.7. In the initial importation application, calculations shall be shown based on the number of volunteers approved by the Agency. However, in repeated importation applications, if the enrollment period for volunteers has not expired, calculations shall be made for the volunteers continuing in the trial together with the volunteers who may be enrolled in the trial. If the enrollment period for volunteers has expired, calculations shall be made only for the volunteers who continue to receive the investigational product. 8.8. In repeated importation applications; information on the quantities of investigational products for which importation has been permitted by the Agency, whose importation has been carried out, which have been distributed to volunteers, which have been lost, if any, and which remain in the warehouse and/or at the trial site, shall be shown separately in the application form in a table format for each investigational product, if there is more than one investigational product. 8.9. In repeated importation applications, where there is investigational product remaining in the warehouse and/or at the trial site, the quantity of investigational product requested for importation shall be determined taking into account the quantity of remaining investigational

product. 8.10. The procedures carried out/to be carried out regarding lost investigational products shall be specified in the application form. 8.11. The sponsor or the legal representative of the sponsor shall submit to the Agency, within 90 days following the last visit of the last patient, a report containing the quantities of imported investigational products, used by volunteers, lost, and remaining from the trial, as well as the procedures carried out/to be carried out regarding the lost investigational products and the remaining investigational products. 9. EVALUATION PERIOD 9.1. Applications shall be evaluated within 15 working days from the date of application. 9.2. If the importation request is deemed appropriate, an assessment is created for the payment of the required document fee. 9.3. Within 5 working days following the payment of the required fee by the applicant, the proforma invoice shall be transmitted to the applicant with the necessary endorsement. 9.4. If, as a result of the evaluation of the application, missing documents and/or information are identified, the deficiencies shall be notified to the applicant within the period specified in 9.1. 10. ENTRY INTO FORCE 10.1. This guideline shall enter into force on the date of its approval.