GUIDELINE ON THE IMPORTATION, RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS FOR HUMAN USE TO BE USED IN CLINICAL TRIALS KAD-KLVZ-20

Guideline on the Importation, Return and Destruction of Investigational Products to be Used in Clinical Trials Document No: KAD-KLVZ-20 First Publication Date: 26.02.2020 Revision No: 01 Revision Date: 26.08.2026 Page: 2 / 11

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1. PURPOSE This guideline has been prepared for the purpose of establishing the procedures and principles regarding the importation, return and destruction of investigational products and auxiliary medicinal products for human use to be used in clinical trials permitted to be conducted in our country. 2. SCOPE It covers the procedures and transactions relating to the importation, return and destruction of investigational products and auxiliary medicinal products for human use to be used in clinical trials permitted to be conducted by the Department of Clinical Trials of the Turkish Medicines and Medical Devices Agency (TİTCK). 3. LEGAL BASIS This guideline has been prepared on the basis of Article 508, first paragraph, subparagraph (a) of the Presidential Decree on the Organization of Ministries and Affiliated, Related and Associated Institutions and Organizations and Other Institutions and Organizations No. 4, published in the Official Gazette No. 30479 dated 15/7/2018, and the Regulation on Clinical Trials of Medicinal Products for Human Use, which entered into force upon publication in the Official Gazette No. 32203 dated 27/5/2023. 4. DEFINITIONS 4.1. As used in this guideline; 4.1.1. Investigational Product: A medicinal product for human use that is tested or used as a reference, including placebo, in a clinical trial, 4.1.2. Investigational Products and Auxiliary Medicinal Products for Human Use with Compromised Integrity: Investigational products and auxiliary medicinal products for human use whose packaging, container or primary container-closure system (vial, ampoule, blister, pre-filled syringe, etc.) has been opened, broken, punctured, leaked, contaminated, or whose physical integrity has otherwise been compromised, 4.1.3. Investigational Products and Auxiliary Medicinal Products for Human Use with Uncompromised Integrity: Investigational products and auxiliary medicinal products for human use whose packaging and primary container-closure system are intact and unopened, but which have passed their expiry date, have been deemed unfit for use due to deviation from storage conditions or recall, or whose use has been discontinued by the sponsor due to the termination of the trial, a decision to use a different batch, or similar reasons, 4.1.4. Service Provider: A commercial, academic or other person or organization providing a service used by the sponsor or investigator to perform trial-related activities, 4.1.5. Return: The sending of investigational products and auxiliary medicinal products for human use to the sponsor or to the service provider authorized by the sponsor in relation to the relevant activity, 4.1.6. Destruction: The disposal of investigational products and auxiliary medicinal products for human use by rendering them unusable in accordance with the relevant legislative provisions, 4.1.7. Agency: The Turkish Medicines and Medical Devices Agency (TİTCK), 4.1.8. Pooled Importation: The procurement of investigational products and auxiliary medicinal products for human use, through a single importation transaction, for use in more than one clinical trial, 4.1.9. Proforma Invoice: A document, electronically/wet-signed by the applicant (containing the name and title of the authorized signatory), containing the information contained in the original invoice to be submitted to the relevant customs administration during the registration of the customs declaration, including the type, quantity, estimated price, etc. of the investigational products and/or auxiliary medicinal products for human use. 4.2. The definitions specified in the Good Clinical Practice Guideline and the relevant legislation shall apply. 5. IMPORTATION OF INVESTIGATIONAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS FOR HUMAN USE General Principles 5.1. The importation permit application shall be made, in accordance with the relevant legislation, by the sponsor, the legal representative of the sponsor, or the contracted research organization to which

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the task has been delegated. 5.2. Where the applicant is not the sponsor of the trial, the power of attorney evidencing that the legal representative or contracted research organization that will conduct the importation process has been authorized by the sponsor in this regard must be submitted electronically as an annex to the clinical trial application or as an annex to the first importation permit application. In recurring importation applications, the date and number of the application to which the document was submitted must be indicated in the cover letter. 5.3. Applications for the importation of investigational products and auxiliary medicinal products for human use to be used in clinical trials permitted to be conducted in our country by the Department of Clinical Trials may be made following the approval of the trial by the Department of Clinical Trials. 5.4. For the importation of medical devices that are the subject of the trial, permission must be obtained from the relevant department of the Agency. 5.5. For the importation of investigational products and auxiliary medicinal products for human use subject to control, permission must be obtained from the relevant department of the Agency. 5.6. Investigational products and auxiliary medicinal products for human use whose importation is permitted within the scope of this Guideline may be used only at approved sites and only for participants enrolled in the trial under the approved protocol. 5.7. A single pooled importation permit application may be submitted for the same investigational products and/or auxiliary medicinal products for human use to be used under more than one trial protocol having the same sponsor. In this case, the products for which importation is requested and their quantities must be indicated separately for each trial on a trial-by-trial basis. 5.8. By signing the relevant application form, the applicant undertakes that the information provided in the application form concerning the investigational products and auxiliary medicinal products for human use is accurate. 5.9. The sponsor is responsible for ensuring that the importation, storage, distribution and delivery to the trial sites of the investigational products and auxiliary medicinal products for human use are carried out in accordance with the relevant legislation, and for keeping records in a manner that ensures product traceability. These records must be retained for the period required by the relevant legislation. Application for an importation permit for investigational products and auxiliary medicinal products for human use 5.10. An application is made to the Agency using the cover letter template and application form published on the Agency's website. A signed proforma invoice must be enclosed. 5.11. 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 other information and documents. In the event of any change in this information/documentation, an application must be made to the ethics committee and the Agency in accordance with the relevant legislation regarding such change before submitting the importation permit application, and the processes

Use in Another Trial 5.25. The use of an investigational product or auxiliary medicinal product for human use imported within the scope of a trial in another trial may only be permitted by the Agency in emergency or exceptional circumstances. Cases where interruption of the participant's treatment poses a serious risk to their health or safety, or where the continuity of the participant's treatment cannot be ensured otherwise, may be regarded as emergency circumstances; the existence of patient or public benefit, the requirements of the protection of public health, or an unforeseen delay in the supply of the investigational product may be regarded as exceptional circumstances. 5.26. Prior to the use of an investigational product or auxiliary medicinal product for human use imported within the scope of a trial in another trial, an application must be made to the Agency, including the justification of the situation, the product to be used, the quantity, and information regarding the trial in which the product is planned to be used. The products in question may be used in the relevant trial if deemed appropriate by the Agency. 5.27. The quantity of the investigational product or auxiliary medicinal product for human use whose use in another trial has been permitted by the Agency must be indicated in the relevant field of the application form in subsequent import permit applications for the trial in which the product will be used, and must be taken into account in the calculation of the quantity to be

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imported.

Proforma Invoice 5.28. A proforma invoice must be included as an annex to the application. Proforma invoices must specify the invoice date and/or proforma invoice number, the name of the manufacturer, the names and quantities of the investigational products and auxiliary medicinal products for human use, and the packaging form and package contents. 5.29. The proforma invoice may include the investigational products and auxiliary medicinal products for human use to be used in the trial, as well as the materials required for the administration, use and distribution of these products.

Import Permit Application Assessment Period 5.30. Applications are assessed within 15 working days from the date of application. For clinical trials intended for exceptional circumstances, this period is 3 working days. 5.31. Where the import request is deemed appropriate, an assessment notice is generated for the payment of the required document fee. 5.32. Within 5 working days following the payment made by the applicant, the proforma invoice is endorsed with the required notation and submitted to the applicant. For clinical trials intended for exceptional circumstances, this period is 3 working days. 5.33. Where missing documents and/or information are identified as a result of the assessment of the application, the deficiencies are notified to the applicant within the period specified in Article 5.30.

Fee Schedule 5.34. The fee schedule for import permit applications is determined on the basis of the multiplication of the number of trials in which the investigational products will be used by the number of proforma invoices submitted as annexes to the application for joint import applications, and, for import applications relating to a single trial, on the basis of the number of proforma invoices submitted as annexes to the application.

Storage of Investigational Products and Auxiliary Medicinal Products for Human Use 5.35. Investigational products and auxiliary medicinal products for human use imported with Agency permission may, following completion of the importation, be dispatched directly to the trial sites or, depending on the scope of the activity to be conducted, to facilities authorized by the Agency for secondary packaging and storage of imported products. 5.36. It is the responsibility of the investigator to store the investigational products and auxiliary medicinal products for human use held at the trial sites under appropriate conditions.

6. RETURN OF INVESTIGATIONAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS FOR HUMAN USE 6.1. Upon the sponsor's request, investigational products and auxiliary medicinal products for human use may be returned from the trial site and/or, depending on the scope of the activity to be conducted, from facilities authorized by the Agency for secondary packaging and storage of imported products, to the sponsor or to the service provider authorized by the sponsor for the relevant activity. Returns to be made abroad cover only investigational products and auxiliary medicinal products for human use whose importation has been permitted by the Agency and which have actually been imported. 6.2. Investigational products and auxiliary medicinal products for human use that are no longer needed for use within the scope of the trial or that are not suitable for use must be kept physically separated from usable stock and appropriately labeled. The quarantine, segregation and labeling operations are carried out by authorized personnel in accordance with the standard operating procedures of the trial site or the relevant warehouse and the trial documents or instructions of the sponsor. The labeling must include a clear warning such as "QUARANTINED / DO NOT USE" or similar that prevents the use of the relevant products. The decision regarding the return or destruction of the products must be made by the sponsor, taking into account the following considerations. 6.2.1. It is essential that investigational products and auxiliary medicinal products for human use whose integrity has been compromised, particularly in cases where their transport may pose a risk to human or environmental health, be destroyed in our country in accordance with the relevant legislative requirements. However, where requested by the sponsor, and provided that the transport of these products does not pose a risk to human or environmental health and/or the necessary measures for their safe transport have been taken, the products in question may be returned to the locations

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designated by the sponsor, subject to compliance with the relevant legislative requirements. 6.2.2. Investigational products and auxiliary medicinal products for human use whose integrity has not been compromised but which are no longer needed for use or are not suitable for use may be returned from the trial site and/or, depending on the scope of the activity to be conducted, from facilities authorized by the Agency for secondary packaging and storage, to the sponsor or to the service provider authorized by the sponsor for the relevant activity. 6.3. All responsibility for the return of investigational products and auxiliary medicinal products for human use lies with the sponsor, and the necessary measures must be taken to maintain the quality, safety and traceability of the products. 6.4. The return of investigational products and auxiliary medicinal products for human use must be carried out in a manner that ensures the maintenance of the quality, safety and traceability of the products, in accordance with the requirements set out in the relevant legislation, the trial protocol and the relevant trial documents. 6.5. The names of the products to be returned, their pharmaceutical form, batch number, expiry date, the quantities returned, and the reason for return must be recorded.

8.2.1. In the event of a justified circumstance that renders it impossible to submit the Closure Report within the specified period, an extension of time must be requested from the Agency, stating the justification, before the expiry of the 90-day period.

8.3. In the Closure Report, for each investigational product and auxiliary medicinal product for human use separately, the following information regarding the product movements carried out during the trial and the final status of the products must be submitted, and the specified documents must be attached to the Closure Report:

8.3.1. The basic quantity required for the investigational product and auxiliary medicinal product for human use, 8.3.2. The safety margin deemed appropriate by the Agency, 8.3.3. The total quantity on which the importation is based, 8.3.4. The total quantity for which importation has been authorized, 8.3.5. The total quantity actually imported, 8.3.6. The quantity administered to/used by participants, 8.3.7. The quantity remaining at sites authorized by the Agency for secondary packaging and storage, according to the trial site and/or the scope of the activity to be carried out, 8.3.8. If any, the quantity of products lost, the reason for the loss, the description of the event or circumstance that led to the loss, and, where necessary, the corrective and preventive measures taken or planned to prevent recurrence of the loss, 8.3.9. The quantity returned to the sponsor, 8.3.10. The quantity of products that have been destroyed, set aside or dispatched for destruction but whose destruction process has not yet been completed, 8.3.11. Where applicable, the quantity authorized by the Agency for use in another trial, 8.3.12. Where applicable, the quantity obtained from another trial with the authorization of the Agency, 8.3.13. If any, an explanation of matters not covered in the above subparagraphs, 8.3.14. The records demonstrating that the investigational products and/or auxiliary medicinal products for human use have been delivered to a destruction facility for the purpose of destruction, and/or that the destruction has been completed by the destruction facility, and/or that they have been included in the general hospital medicinal product destruction process, and/or that it has been completed.

8.4. The quantities of investigational products and auxiliary medicinal products for human use presented in the Closure Report must be consistent with one another, and the traceability of all product movements must be ensured. In the event of any discrepancy between the quantities, the reason for the discrepancy must be explained.

9. TRACEABILITY

9.1. Records and documents relating to the following information verifying the product movements and the final status of the products must be kept by the sponsor and submitted to the Agency upon request:

9.1.1. Records showing the import authorizations granted by the Agency and the quantities of importation actually carried out, 9.1.2. Records showing the shipment and distribution of the investigational products and auxiliary medicinal products for human use to the trial sites and/or to sites authorized by the Agency for secondary packaging and storage, 9.1.3. Records showing the

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returns,

10. PRODUCT SAFETY MONITORING

10.1. It is the responsibility of the sponsor to monitor the "Medicinal Product Recall" announcements published on the official website of the Agency concerning the recall of defective medicinal products for human use, or medicinal products suspected of being defective, from specific distribution chains by the marketing authorization/permit holder. In the event that a recall decision has been published for an investigational product or auxiliary medicinal product for human use used within the scope of the trial, the necessary measures must be taken by the sponsor in accordance with the relevant legislation.

10.2. It is the responsibility of the sponsor to monitor, through the "List of Authorized Products" and the "List of Revoked Authorizations" published on the official website of the Agency, the information regarding the authorization status of authorized medicinal products for human use. In the event that the authorization of an investigational product or auxiliary medicinal product for human use used within the scope of the trial is suspended or revoked, the necessary measures must be taken by the sponsor in accordance with the relevant legislation.

11. ENTRY INTO FORCE This guideline enters into force on the date of its approval.

12. REVISION HISTORY

No. Subject Rev. No. Rev. Date 1 Initial publication 00 26.02.2020 2 In line with current legislation and implementation needs, the scope of the guideline has been expanded to include auxiliary medicinal products for human use; the provisions regarding the importation and storage of investigational products have been updated; provisions regarding the return, destruction and closure reporting processes to the sponsor have been added; and the title of the guideline has been changed. 01 26.08.2026

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