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GUIDELINE ON RELIANCE PRACTICES IN CLINICAL TRIAL APPLICATIONS KAD-KLVZ-24

First Version Effective Date 01.09.2022 1st Revision Effective Date 05.06.2024 2nd Revision Effective Date 14.11.2025

TABLE OF CONTENTS

1. PURPOSE
2. SCOPE
3. LEGAL BASIS
4. DEFINITIONS and ABBREVIATIONS
5. ASSESSMENT OF THE GOOD LABORATORY PRACTICE CERTIFICATE WITHIN THE SCOPE OF RELIANCE PRACTICES
6. ASSESSMENT OF THE GOOD CLINICAL PRACTICE INSPECTION REPORT WITHIN THE SCOPE OF RELIANCE PRACTICES
7. ASSESSMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER WITHIN THE SCOPE OF RELIANCE PRACTICES
8. ASSESSMENT OF THE MANUFACTURING SITE PERMIT / GOOD MANUFACTURING PRACTICE CERTIFICATE WITHIN THE SCOPE OF RELIANCE PRACTICES
9. ASSESSMENT OF THE USE OF AUXILIARY MEDICINAL PRODUCTS FOR HUMAN USE WITHIN THE SCOPE OF RELIANCE PRACTICES
10. ENTRY INTO FORCE
11. EXECUTION
12. REVISION RATIONALE

1. PURPOSE

1.1. The purpose of this Guideline is to set out the procedures and principles regarding reliance practices taken as the basis in the assessment of clinical trial applications.

2. SCOPE 2.1. This Guideline covers the assessment, within the scope of reliance practices, of relevant decisions/published reports issued by other medicines authorities or regional/international organisations with standards comparable to those of the Agency, which are taken as the basis in the assessment of clinical trial applications. 2.2. The Agency and the relevant ethics committee may request additional information/documents where deemed necessary.

3. LEGAL BASIS 3.1. This Guideline has been prepared based on the Regulation on Clinical Trials of Medicinal Products for Human Use, which was published in the Official Gazette No. 32203 dated 27/5/2023 and entered into force, the Regulation on Manufacturing Sites of Medicinal Products for Human Use published in the Official Gazette No. 30217 dated 21/10/2017, and the Regulation on the Licensing of Medicinal Products for Human Use published in the Official Gazette No. 31686 dated 11/12/2021.

4. DEFINITIONS and ABBREVIATIONS 4.1. In this Guideline; 4.1.1. Investigational Medicinal Product: a medicinal product for human use that is tested or used as a reference in a clinical trial, including placebo, 4.1.2. Investigational Medicinal Product Dossier: the document containing

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information on the quality, manufacture and control of the investigational medicinal product, together with data obtained from non-clinical studies and from its clinical use, including clinical trials, 4.1.3. Application Guideline: the Guideline on Clinical Trial Applications Made to the Turkish Medicines and Medical Devices Agency, Department of Clinical Trials (KAD-KLVZ02), 4.1.4. Active Substance: the substance or mixture of substances that constitutes the active component of the product, planned to be used in the manufacture of an investigational medicinal product (medicinal product for human use), which, when used in its manufacture, exerts a pharmacological, immunological or metabolic action with a view to correcting, improving or modifying physiological functions or making a medical diagnosis, 4.1.5. Reliance: the act whereby the Agency, within a given jurisdiction, in reaching its own decision, takes into account or gives significant weight to reliable information such as evaluations performed by another regulatory authority or a trusted institution, 4.1.6. GMP: good manufacturing practices,

4.1.7. GCP: good clinical practice, 4.1.8. GLP: good laboratory practice, 4.1.9. Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), 4.1.10. Modified Licensed Investigational Medicinal Product: a medicinal product for human use that has been authorised by the Competent Authorities and whose particulars underlying the marketing authorisation have been modified, 4.1.11. Unmodified Licensed Investigational Medicinal Product: a medicinal product for human use that has been authorised by the Competent Authorities and whose particulars underlying the marketing authorisation have not been modified, 4.1.12. Manufacture (production): the weighing, subdivision, processing, primary packaging operations, secondary packaging operations of starting materials used in the manufacture of medicinal products for human use and/or active substances, including clinical trial products, their conversion into finished products, the controls related thereto, and batch release activities, 4.1.13. Qualified Person: the person possessing the scientific/technical qualifications specified in Directive 2001/83/EC of the European Parliament and of the Council who fulfils the responsibilities attributed to them, 4.1.14. Qualified Person Declaration: the declaration issued by the Qualified Person attesting that, for investigational medicinal products manufactured in facilities abroad, the manufacturing standards of the investigational medicinal products in question comply with internationally accepted good manufacturing practice (GMP) standards, 4.1.15. Competent Authority: the Turkish Medicines and Medical Devices Agency (TİTCK), together with the ICH (International Council for Harmonisation) founding member competent authorities (the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA)) or its permanent member competent authorities (the Swiss National Medicines Authority (Swissmedic) and the Canadian National Medicines Authority (Health Canada)), the Australian National Medicines Authority (TGA) or the United Kingdom National Medicines Authority (MHRA), 4.1.16. Regulation: the Regulation on Clinical Trials of Medicinal Products for Human Use, which was published in the Official Gazette No. 32203 dated 27/5/2023 and entered into force, shall mean. 4.2. The definitions set out in the Regulation on Clinical Trials of Medicinal Products for Human Use and in the relevant legislation shall also apply to this Guideline.

5. ASSESSMENT OF THE GOOD LABORATORY PRACTICE CERTIFICATE WITHIN THE SCOPE OF RELIANCE PRACTICES 5.1. Non-clinical pharmacological and toxicological studies shall be conducted in accordance with the provisions laid down in the Regulation on the Principles of Good Laboratory Practice (GLP), the Harmonisation of Test Facilities and the Inspection of Good Laboratory Practice and Studies, published in the Official Gazette No. 27516 dated 9/3/2010. 5.2. A GLP certificate demonstrating compliance with internationally accepted GLP standards shall be submitted.

5.3. Where the documents submitted within this scope are prepared in a language other than Turkish or English, sworn translator and notarized Turkish or English translations of the documents in question must also be submitted, in addition to the documents themselves.

6. EVALUATION OF THE GOOD CLINICAL PRACTICE INSPECTION REPORT WITHIN THE SCOPE OF RELIANCE PROCEDURES 6.1. As stated in the Application Guidance, the investigational

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medicinal product dossier shall include a declaration that the clinical trials applied for to the Agency are conducted in accordance with the principles of good clinical practice (GCP). However, where deemed necessary, the Agency may request the inspection report conducted by other health authorities confirming compliance with GCP, or GCP inspections may be carried out by the Agency. 6.2. Provided that no situation contrary to the legislation of our country is identified, where the reports regarding the GCP inspections conducted by the National Competent Authority for the clinical trial in question are submitted and where the inspection reports state that the inspected sites/trials or the data pertaining to the trial are in compliance with GCP, GCP inspections shall not be conducted by the Agency. 6.3. Where reports regarding GCP inspections carried out by health authorities other than the National Competent Authority are submitted, GCP inspections shall be conducted by the Agency in accordance with the requirements of the relevant guidance.

7. EVALUATION OF THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER WITHIN THE SCOPE OF RELIANCE PROCEDURES 7.1. In cases where the investigational medicinal products are not authorized by the National Competent Authorities, the investigational medicinal product dossier (IMPD) prepared in accordance with the "Guideline on the Chemical and Pharmaceutical Quality Requirements for Human Medicinal Products Used in Clinical Trials" and the "Guideline on the Quality Requirements for Biological Medicinal Products Used in Clinical Trials" shall be submitted. Where a signed and apostilled document demonstrating that the IMPD submitted to the Agency has been reviewed and found acceptable by the National Competent Authorities with the same date and version number is submitted, the relevant IMPD shall not be re-evaluated by the Agency and shall be deemed acceptable. The apostille certification must be issued by the country in which the relevant document was prepared. 7.2. In cases where the investigational medicinal products are authorized by the National Competent Authorities and no modification has been made to the particulars of the marketing authorization (not modified), it is sufficient to submit the name of the marketing authorization holder and the marketing authorization number (including equivalent information such as a copy of the summary of product characteristics / summary of product characteristics or prescribing information). 7.3. In cases where the investigational medicinal products are authorized by the National Competent Authorities and no modification has been made to the particulars of the marketing authorization (not modified), but only repackaging is carried out without altering the primary packaging, the information regarding the site(s) where the repackaging/relabeling operations are performed must be submitted in a simplified IMPD, in addition to the information/documents specified in Article 7.2 of this guideline.

7.4. In cases where the investigational medicinal products are authorized by the National Competent Authorities and modifications have been made to the particulars of the marketing authorization (modified), the relevant sections of the IMPD shall be submitted, depending on the degree of the modification made, in line with the requirements set forth in the "Guideline on the Chemical and Pharmaceutical Quality Requirements for Human Medicinal Products Used in Clinical Trials" and the "Guideline on the Quality Requirements for Biological Medicinal Products Used in Clinical Trials". In such a case, where a signed and apostilled document demonstrating that the IMPD submitted to the Agency has been reviewed and found acceptable by the National Competent Authorities with the same date and version number is submitted, the relevant IMPD shall not be re-evaluated by the Agency and shall be deemed acceptable. The apostille certification must be issued by the country in which the relevant document was prepared. 7.5. For auxiliary human medicinal products, the appropriate information/documents shall be submitted pursuant to Articles 7.2, 7.3 or 7.4 of this guideline.

8. EVALUATION OF THE MANUFACTURING SITE PERMIT / GOOD MANUFACTURING PRACTICE CERTIFICATE WITHIN THE SCOPE OF RELIANCE PROCEDURES 8.1. The documents submitted to the Agency within the scope of good manufacturing practice (GMP) shall be valid/up to date. 8.2. Where the documents submitted for the manufacturing site(s) are prepared in a language other than Turkish or English, sworn translator and notarized Turkish or English

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translations of the documents in question must also be submitted, in addition to the documents themselves. 8.3. Except for the Manufacturing Site Permits/GMP certificates issued by the Agency, where the Manufacturing Site Permit/GMP certificate submitted for the manufacturing site(s) is not published in a publicly accessible database, a signed and apostilled Manufacturing Site Permit and/or GMP certificate shall be submitted. The apostille certification must be issued by the country in which the relevant document was prepared. 8.4. Within the scope of the GMP documentation requirements for the active substance(s) used in the manufacture of the investigational medicinal products, the matters set out below shall be fulfilled. 8.4.1. For investigational medicinal products containing active substance(s) obtained by chemical synthesis, the active substance(s) and, where applicable, the intermediate(s)/product(s) used in the manufacturing process of the active substance(s) shall be manufactured in accordance with internationally accepted GMP standards.

8.4.2. For investigational products containing active substance(s) of biological origin, the provisions set forth in Articles 8.3 or 8.5 of this Guide shall apply to the premises where the active substance(s) and, where applicable, the intermediate/product(s) used in the manufacturing process of the active substance(s) are manufactured. 8.5. For all manufacturing activities carried out at manufacturing sites of investigational products not authorized by the Competent Authorities, information/documents complying with any of the following shall be submitted. 8.5.1. Where the investigational products are manufactured at domestic sites, submission of the Manufacturing Site Authorization Certificate, issued by the Agency and covering manufacturing activities for Medicinal Products for Human Research Purposes as set out in ANNEX 2, pertaining to the manufacturing site(s); 8.5.2. Where the investigational products are manufactured at sites abroad and the Manufacturing Site Authorization Certificate/GMP certificate of the said site(s) is published in a publicly accessible database, submission of the Manufacturing Site Authorization Certificate/GMP certificate of the manufacturing site(s) and/or the Manufacturing Site Authorization Certificate number/GMP certificate number; 8.5.3. Where the investigational products are manufactured at sites abroad, submission of the Qualified Person Declaration, issued by the Qualified Person responsible for batch release of the investigational products at a site located in the country of the Competent Authorities, stating that the GMP standards at the manufacturing site(s) are equivalent to internationally recognized GMP standards, and such Declaration shall be kept ready for submission to the Agency upon request, together with reports on inspections carried out by the Qualified Person at the relevant manufacturing site(s); 8.5.4. For the clinical trial applied for, submission of the signed and apostilled clinical trial authorization documents issued by the Competent Authorities, and it shall be warranted that the investigational product to be used in our country within the scope of the clinical trial is manufactured at the same manufacturing site as the investigational product to be used in the country of the Competent Authority granting the authorization. The apostille certification must be issued by the country in which the relevant document was issued. 8.6. For investigational products authorized by the Competent Authorities and auxiliary medicinal products for human use, the following shall be fulfilled within the scope of GMP documentation requirements. 8.6.1. For unmodified authorized investigational products and auxiliary medicinal products for human use, no document shall be requested regardless of the manufacturing site. However, where only repackaging and/or labelling is required without altering the primary packaging, the provisions set forth in Article 8.5 of this Guide shall also apply, for the sites where packaging and labelling are carried out, to unmodified authorized investigational products and auxiliary medicinal products for human use.

8.6.2. For modified authorized investigational products and auxiliary medicinal products for human use, the provisions set forth in Article 8.5 of this Guide shall apply to the site(s) where the relevant manufacturing activities are carried out, depending on the extent of the modification. 8.7. During the evaluation of initial clinical trial applications or the conduct of clinical trials already authorized in our country, the Agency reserves the right to conduct an inspection (on-site inspection/remote inspection/hybrid inspection/risk-based inspection) at the manufacturing

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site(s) where the investigational products are manufactured, and, where deemed necessary, to suspend/terminate the trial (suspend enrollment/discontinue treatment) until the said inspections are concluded.

9. EVALUATION OF THE USE OF AUXILIARY MEDICINAL PRODUCTS FOR HUMAN USE WITHIN THE SCOPE OF COMPASSIONATE USE PRACTICES 9.1. Pursuant to the Regulation, auxiliary medicinal products for human use shall, in principle, be authorized in our country. 9.2. However, provided that the applicant submits reasonable justifications, the use, as auxiliary medicinal products for human use, of medicinal products for human use authorized by the Competent Authority and used in accordance with the particulars of the marketing authorization may be accepted by the Agency. 9.3. The relevant provisions set forth in Articles 7 and 8 of this Guide shall also apply to auxiliary medicinal products for human use.

10. ENTRY INTO FORCE This Guide shall enter into force upon approval by the President of the Agency.

11. EXECUTION This Guide shall be executed by the President of the Agency.

12. RATIONALE FOR REVISION Revision No Revision Date Rationale and Explanations 01 05.06.2024 Articles 6 and 8 have been updated in line with the requirements of the new Regulation. 01 05.06.2024 Articles 7 and 9 have been added in line with the requirements of the new Regulation. 01 05.06.2024 A general review and updates have been carried out in line with the requirements of the new Regulation. 02 14.11.2025 The 'Definitions' section has been updated.

02 14.11.2025 An amendment has been made in the section 'Evaluation of the Good Laboratory Practice Certificate within the Scope of Compassionate Use Practices'. The requirement that "a GLP certificate issued by OECD member countries must be submitted" has been updated to "internationally recognized". 02 14.11.2025 The section 'Evaluation of the Investigational Product Dossier within the Scope of Compassionate Use Practices' has been updated in accordance with the requirements of the Guideline on Chemical and Pharmaceutical Quality Requirements of Medicinal Products for Human Use in Clinical Trials and the Guideline on Quality Requirements of Biological Medicinal Products Used in Clinical Trials. 02 14.11.2025 The section 'Evaluation of the Manufacturing Site Authorization Certificate / Good Manufacturing Practice Certificate within the Scope of Compassionate Use Practices' has been elaborated for active substance(s) obtained by chemical synthesis and active substance(s) of biological origin, and the requirements for investigational products have been updated.

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