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GUIDELINE ON RISK-BASED GOOD CLINICAL PRACTICE INSPECTIONS

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GUIDELINE ON RISK-BASED GOOD CLINICAL PRACTICE INSPECTIONS

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1. Purpose: The purpose of this guideline is to define and standardize the processes related to risk-based good clinical practice (GCP) inspections. 2. Scope: This guideline covers clinical trials submitted in marketing authorization applications, including bioavailability/bioequivalence studies, ongoing clinical trials, and the institutions, organizations and persons related to such trials. 3. Legal Basis: This guideline has been prepared based on paragraph 1 of Article 22 of the Regulation on Clinical Trials of Medicinal Products and Biological Products, which was published in the Official Gazette No. 28617 dated 13.04.2013 and entered into force (Amended: OG 13/09/2015-29474). 4. Abbreviations: BY/BE Bioavailability/Bioequivalence ESY Electronic Process Management, Faz 1 (Phase 1) Phase 1 clinical trials, İKU (GCP) Good Clinical Practice, Kurum (Agency) Turkish Medicines and Medical Devices Agency (TİTCK), SAK (CRO) Contract Research Organization. 5. General Provisions: GCP inspections may be carried out in any of the following circumstances: - Before, during or after the conduct of a clinical trial, - For the purpose of verifying a marketing authorization application, - For follow-up purposes after authorization. Any clinical trial included in the marketing authorization application dossier may be subject to inspection. In this context, a GCP inspection may be conducted "for cause" or within the scope of a routine inspection. GCP inspection requests to be made by the Agency's Department of Drug Licensing and/or Department of Herbal and Supplementary Products are determined based on the risk assessment to be performed by the relevant departments. The purpose of such GCP inspections: - To determine whether the clinical trial has been conducted in accordance with the relevant legislation and the GCP Guideline, - To provide answers in cases where it has been determined that answers to questions arising during the evaluation process can best be obtained through inspection,

- To determine whether the data presented in the dossier are reliable and accurate. GCP inspections may be triggered for various reasons: - To verify the GCP compliance declaration, - For a more detailed examination of the trial with respect to the following matters: o The importance and risk status of the trial in the application, o Inclusion of vulnerable subjects in the trial or other ethical concerns, o Concerns related to the investigational medicinal product (IMP), o Concerns regarding the reliability and accuracy of the data (e.g., in case of an unusual enrollment (recruitment) program, when efficacy or safety results are inconsistent with the results of other trials, when the results of one site differ significantly from the others, when serious findings were identified in a previous GCP inspection of the site and/or organization and/or GCP non-compliance has been continuously reported).

Furthermore, the provisions of the "Guideline on the Definition of Triggers and the Scope of Routine and/or For-Cause Inspections" and the "Guideline on Triggers for Inspections of Bioavailability/Bioequivalence Studies", which have been prepared to provide an overview of potential triggers that may be identified at different stages of the evaluation process, shall be taken into consideration.

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6. Routine Inspections: Routine GCP inspections are inspections conducted for the purpose of routine verification of GCP compliance, without a specific trigger or concern. In routine GCP inspections, the marketing authorization application, the clinical trial and the trial sites may be selected for inspection as a result of the risk assessment to be performed taking into account the matters specified in the "Guideline on the Definition of Triggers and the Scope of Routine and/or For-Cause Inspections" and the "Guideline on Triggers for Inspections of Bioavailability/Bioequivalence Studies". Inspections of phase 1 and BA/BE sites operating in our country, subsequent to their initial opening inspections, are carried out within the scope of routine inspections taking into account the matters specified in the "Guideline on the Definition of Triggers and the Scope of Routine and/or For-Cause Inspections" and the "Guideline on Triggers for Inspections of Bioavailability/Bioequivalence Studies". Within the scope of routine inspections, the selection of the dossier for marketing authorization applications of generic and original medicinal products for human use is made on a risk-based basis by the Department of Drug Licensing and/or the Department of Herbal and Supplementary Products. The Department of Drug Inspection may be contacted when determining the sites to be inspected and the scope of the inspection. In order to ensure the best use of the available inspection resources, the matters specified in the aforementioned guidelines are taken into account. By the aforementioned Departments

pursuant to the inspection request made, the decision on whether the inspection is required shall be taken by the Deputy Presidency of Inspection Services. The inspection request is sent by the Department of Drug Licensing and/or the Department of Herbal and Supplementary Products to the Deputy Presidency of Inspection Services via the ESY system. The inspection request shall explicitly include the reasons and scope of the inspection, the site/sites to be inspected, a list of specific questions to be addressed during the inspection, if any, and other matters related to the inspection. Pursuant to the inspection request made by the aforementioned Departments, the decision on whether the inspection is required shall be taken by the Deputy Presidency of Inspection Services, also taking into account the inspection resources. Following the decision on inspection, the inspection planning shall be carried out by the Presidency of the Drug Inspection Department. In order to include ongoing clinical trials in the routine inspection programme, the inspection request shall be sent to the Deputy Presidency of Inspection Services by the Agency's Presidency of the Clinical Trials Department via the ESY system, taking into account the relevant provisions of the "Guideline on the Definition of Triggers and Scope of Routine and/or For-Cause Inspections". Pursuant to the inspection request made by the aforementioned Department, the decision on whether the inspection is required shall be taken by the Deputy Presidency of Inspection Services, also taking into account the inspection resources. Following the decision on inspection, the inspection planning shall be carried out by the Presidency of the Drug Inspection Department.

7. For-Cause Inspections: These types of inspections are triggered inspections requested by the assessors (Department of Drug Licensing and/or Department of Herbal and Supplementary Products) due to a concern about a deviation from good clinical practice (GCP) in all clinical trials conducted with a medicinal product for human use during the marketing authorisation application evaluation process, or in a study conducted at a specific site. In addition, for ongoing studies, an inspection request may also be made by the Presidency of the Clinical Trials Department due to a concern about a deviation from GCP. The inspection request, which explicitly includes the reasons and scope of the inspection with regard to the triggers defined for the clinical trial and trial site/sites, the site/sites to be inspected, a list of specific questions to be addressed during the inspection, if any, and other matters related to the inspection, is sent to the Deputy Presidency of Inspection Services by the Department of Drug Licensing, the Department of Herbal and Supplementary Products and/or the Presidency of the Clinical Trials Department via the ESY system. Pursuant to the inspection request made by the aforementioned Departments, the decision on whether the inspection is required shall be taken by the Deputy Presidency of Inspection Services, also taking into account the inspection resources. Following the decision on

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inspection, the inspection planning shall be carried out by the Presidency of the Drug Inspection Department.

8. Notification of Inspections: In GCP inspections carried out within the scope of routine inspections, the sponsor, the CRO, the investigator and/or other relevant parties involved in the trial may be notified in advance of the planned inspection date. "For-Cause" inspections may be either announced in advance or carried out unannounced.

9. Miscellaneous and Final Provisions: 9.1. Entry into Force: This Guideline enters into force upon the approval of the President of the Agency.

9.2. Enforcement: The provisions of this Guideline shall be enforced by the President of the Agency.

REVISION HISTORY Revision No Revision Date Reasons and Explanations 01 15.11.2022 Aligned with the guideline template determined within the scope of the Agency's quality system.

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