BIYOYARARLANIM BIYOEŞDEĞERLIK ÇALIŞMALARININ DENETIMLERI İÇIN TETIKLEYICILER HAKKINDA KILAVUZ_ENG.VERS

Guideline on Triggers Regarding Inspections of Bioavailability/Bioequivalence Studies

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1. Purpose: This guideline's purpose is to outline the triggers for inspections regarding bioavailability/bioequivalence (BI/BE) studies submitted with generic product marketing authorisation applications. 2. Scope: This guideline addresses bioavailability/bioequivalence studies filed during the marketing authorisation applications of generic pharmaceutical products. 3. Basis: Article 22 of the Implementing Regulation on Clinical Trials of Medicinal And Biological Products (Amended: OG-25/6/2014-29041), published in the Official Gazette dated 13 April 2013 and numbered 28617, served as the foundation for the creation of this guideline. 4. General Considerations: The checklist in this guideline's annex is intended to be utilized by evaluators as they examine BA/BE studies that have been presented as a foundation for marketing authorization of generic medications. It shall be emphasized, however, that this guideline only serves as a general overview for evaluators, allowing them to request an inspection regarding the generic medicines marketing authorization applications files. It does not, therefore, offer an entire list of triggers. It is conceivable that other triggers that are not included in this guideline may be found. The list in the guideline annex is considered a quick scan. The applicant should be contacted first regarding any issue involving missing documents. Evaluators are urged to first speak with the Vice Presidency of Inspectorate if, after completing the checklist, triggers are identified that may have an impact on the accuracy of the data. An activity-specific triggered inspection or a system inspection may be initiated if the applicant is unable to provide sufficient answers regarding the generic medicines marketing authorization application file and there are growing concerns about the quality, accuracy, and reliability of the data. Although several triggers may be defined, only one trigger can be sufficient cause to justify a GCP inspection. Alternative mechanisms to restore confidence may be helpful to advance the application's evaluation if issues brought up concern low or moderate risk areas that do not affect the study's overall quality. These include asking the marketing authorization applicant about the relevant organization's routine system knowledge or bringing up the issue with the Vice Presidency of Inspectorate. Before requesting an inspection, the BA/BE study should be reviewed for compliance with current criteria if it is outdated, e.g five years or older. 5. Miscellaneous and Final Provisions 5.1. Enforcement This guideline goes into effect on the day of approval. 5.2. Execution: The provisions of this guideline are executed by the President of the Turkish Medicines and Medical Devices Agency.

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1. General Inspection Question General Considerations Evaluator's Comment 1. Has the Turkish Medicines and Medical Devices Agency previously inspected the study? A new inspection request shall not be submitted and the results of the prior inspection may be accepted if a clean report is obtained regarding the prior activity inspection (except where new information is available or the previous inspection did not cover all parts of the study).

In general, this application should be rejected if the preceding inspection of the study yielded poor results.

2. Has the Turkish Medicines and Medical Devices Agency previously inspected the center where the (clinical/analytical) study was conducted? A new inspection request shall not be submitted and the results of the prior inspection may be accepted if a clean report is obtained regarding the inspection of the center where the study was conducted (except where new information is available or the previous inspection did not cover all parts of the study).

If the center did not pass the most recent inspection, the Vice Presidency of Inspectorate should be consulted regarding whether the prior inspection results are acceptable for the current

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study or whether a GCP inspection is necessary.

The outcomes of accepting the current study or the requirement for GCP inspection should be discussed with the Vice Presidency of Inspectorate if the center where the study is conducted has never undergone an inspection. The center, however, can be added to the routine inspection checklist if triggers are present.

3. Was the last inspection performed more than three years ago? This should be discussed with the Vice Presidency of Inspectorate in relation to the identification of

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potential triggers. An inspection interval of more than three years is not a trigger by itself. 2. Data Check Questions General Considerations 4. Does the product have any distinctive characteristics? e.g.: Assertive formulations (e.g. Transdermal therapeutic systems) Complex pharmacokinetic profile. Individual pharmacokinetic outcomes in this situation should be carefully scrutinized. e.g. Deviation from individual concentrations, the timing of pharmacokinetic analyzes, plasma concentrations reported at the beginning and end of the analysis period etc.

5. Lack of information, (e.g. Does information about missing validation, analytical, clinical, or other reports, method procedures, and other pertinent procedures, as well as submitted chromatograms, cast doubt on adherence to current criteria and guidelines? The applicant should be contacted first to address any issue regarding any missing documents. Only when a response is submitted and uncertainty about the newly supplied document arises does this issue become an inspection trigger.

6. Are there any general findings that cast doubt on the reliability and caliber of the study data that have been reported? e.g.: The data concerning the study is very clear/very complex When it comes to the active ingredient or the sort of measurement, the amount of missing data or drop-outs falls short of the evaluator's expectations. Lack of credibility/inconsistency of clinical or analytical data provided, Data/results on the product/active substance that differ from those published and known (e.g. distribution and/or characteristics of the volunteers), Conflicting results between studies regarding pharmacokinetic parameters or variability across/among the volunteers The issues that arise should be regarded seriously even though the solutions to these challenges are not always obvious.

In general, problems should be evaluated using an accurate understanding of bioequivalence testing procedures.

In some circumstances, the execution and results of the study might be compared to earlier studies to look for any potential issues.

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The existence of different bioequivalence research that was carried very soon before or after the one that was presented (this may be a positive or a failed study). 3. Specific Inspection 7. Do any observations cast doubt on the accuracy or standard of the data pertaining to volunteers? e.g.: Violation of the inclusion/exclusion criteria, Inconsistency between the frequency and seriousness of adverse effects and the product's established profile. Insufficient detection of dosing timing discrepancies, failure to adhere to the protocol's diet and exercise requirements

8. Are there any findings that cast doubt on the validity or caliber of sample processing, or on the analysis of volunteer samples? e.g.: Contradictions between the quantity of samples that were taken, examined, and reported, Inadequate information to confirm the samples' integrity (e.g. regarding storage, transport and stability) Lack of adequate definition for the re-analysis of the samples and for how to manage missing samples, Sampling times, Re-analysis of many samples, Re-injection of calibrators or QC, Failure to inject the samples at proper intervals. Sample re-analysis for pharmacokinetic reasons, Indications of improper manual chromatogram reintegration. The Vice Presidency of Inspectorate shall be consulted if it is felt that issues have a low compliance to current requirements, even though some of the issues raised can be resolved by

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seeking more information.

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9. Do any findings cast doubt on the accuracy or reliability of the validation of analytical methods? e.g.: Failure to fully validate the bioanalytical method prior to analysis of study samples. Inadequate method validation data and admission criteria, Inconsistency between the data presented and disclosed and planned methodologies (e.g., retention times, chromatogram descriptors, run sequence/order), Removing of QC samples from statistical analysis. Instead of an inspection request, all results must first be recalculated (or sought from the applicant) if QC samples are excluded in statistical analysis.

10. Are there any findings that cast doubt on the accuracy or reliability of the statistical analysis? For example: Failure to submit a separate report for pharmacokinetic and statistical analyses, not including statistical software output files, Inaptness of software used for pharmacokinetic and statistical analysis (e.g. unknown, not obtained from a commercial source) Inconsistencies between the text summaries and summaries and individual data in the table. The actual power values for Cmax and or AUC are below 0.65 and confidence limits approaching the 80-125 limits by less than 1%. The Vice Presidency of Inspectorate shall be consulted if it is felt that issues have a low compliance to current requirements, even though some of the issues raised can be resolved by seeking more information.

EVALUATOR'S FINAL COMMENTS

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