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PHARMACOVIGILANCE INSPECTION GUIDE İDD-KLVZ-04

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1. INTRODUCTION

1.1. Purpose and Scope

This guide is explanatory and guiding with regard to the planning, conduct, reporting and follow-up of pharmacovigilance inspections in our country.

The purpose of this guide is to establish the procedures and principles regarding the operation of pharmacovigilance inspections carried out to ensure compliance of marketing authorization holders, contracted pharmacovigilance service organizations and other relevant institutions/organizations with the legislation.

Through pharmacovigilance inspections, it is intended:

To determine whether marketing authorization holders, contracted pharmacovigilance service organizations carrying out pharmacovigilance activities on behalf of marketing authorization holders, and other relevant organizations possess the system, personnel, facilities and equipment to meet pharmacovigilance requirements, To identify, record and evaluate violations that may pose a risk to public health, and where necessary, to apply administrative sanctions based on the inspection results.

Marketing authorization holders, healthcare institutions and organizations, contracted pharmacovigilance service organizations and other relevant organizations are obliged to take all

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necessary measures for the proper conduct of pharmacovigilance inspections; their responsibilities relating to inspections include, but are not limited to, the following:

To be ready for inspection at all times and to keep available the personnel involved in pharmacovigilance activities, the facility and all relevant documents during the inspection, To submit to the Agency any information and documents deemed necessary during the preparation process for the inspection within the specified period, To submit to the inspection team any information and documents requested during the inspection, To prepare a corrective and preventive action plan regarding the non-conformities identified during the inspection and to remedy the deficiencies in a timely manner, To ensure compliance with the legislation in the post-inspection process and to notify the Agency of the changes made.

1.2. Legal Basis This guide has been prepared based on: a) Article 3, paragraph (k) of the Fundamental Law on Health Services No. 3359 dated 7/5/1987, b) Article 352, first paragraph, paragraph (d) of Presidential Decree No. 1 No. 30474 dated 10/07/2018, c) Article 508, first paragraph, paragraphs (a) and (ğ) of Presidential Decree No. 4 No. 30479 dated 15/07/2018, ç) Article 32 of the Regulation on the Safety of Medicinal Products No. 28973 dated 15/04/2014.

1.3. Definitions

As used in this guideline;

a) ICSR: Individual Case Safety Report, b) GCP: Good Clinical Practice, c) GDP: Good Distribution Practice, ç) GMP: Good Manufacturing Practice, d) GPvP/GVP: Good Pharmacovigilance Practice, e) Agency: Turkish Medicines and Medical Devices Agency (TİTCK), f) MedDRA: Medical Dictionary for Regulatory Activities developed by the International Conference on Harmonisation, g) CPO: Contracted Pharmacovigilance Service Organization,

2. TYPES OF INSPECTIONS

2.1. Systems and Product Inspections

Pharmacovigilance systems inspections are carried out for the purpose of on-site examination of the system, procedures, personnel and facilities, and determining compliance of the activities with the legislation. During the inspection, product-based samples may be used in order to verify the operability of the system and to assess compliance.

Product-related pharmacovigilance inspections focus primarily on product-specific activities and product-specific pharmacovigilance issues rather than examination of the general system. However, within the framework of a product-related inspection, matters relating to the system as a whole (e.g. the system used for the product subject to the inspection) may also be examined.

2.2. Routine and Targeted Inspections

Routine pharmacovigilance inspections are planned in advance and included in the inspection programme. Although no specific triggering factors are required for these inspections, a risk-based approach is followed for the efficiency of the inspection activities. Routine inspections are generally systems inspections. Special situations (e.g. situations such as an inspection being requested within the Agency or a complaint being received) may be added to the scope of routine inspections.

Targeted inspections are initiated upon the emergence of a triggering factor. Targeted inspections may be conducted in order to focus on specific pharmacovigilance processes, or to examine predefined compliance problems or their effects on a particular product. Depending on the triggering factors, the entire system may be inspected. Targeted inspections may be carried out when one or more of the following triggering situations occur, without being limited thereto:

Benefit/risk balance of the product; o When the benefit/risk balance needs to be examined in more detail through an inspection, o When a risk is identified, or when there is a delay or omission in the reporting of a risk, or when there is a change in the benefit/risk balance, o When

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information containing pharmacovigilance issues/concerns is reported to the Agency, o When a non-compliance is detected in the pharmacovigilance activities monitored by the Agency or when product safety issues are identified, o When information regarding pharmacovigilance issues is shared with the public without prior or simultaneous notification to the Agency; Reporting requirements; o Delay or omission in reporting, o Reports being incomplete or of poor quality, o Inconsistencies between reports and source documents; Agency requests; o Omission in providing the information or data requested within the time period determined by the Agency, o Submission of insufficient data in meeting the information and documents requested by the Agency; Fulfilment of commitments; o Delay or omission in fulfilling risk management plan commitments, o Delay or omission in fulfilling specific requirements for monitoring product safety, o Deficiency or quality issue in the reports requested under specific obligations; Inspections; o Inadequate practices or delays in corrective and preventive actions, o Identification of a risk related to product safety emerging in other inspections (GCP, GMP and GDP), o Non-compliances identified in inspections conducted by other authorities; Others; o Identification of non-compliance as a result of the review of the pharmacovigilance system master file, o Non-compliance information received from other authorities that is not related to an inspection.

2.3. Announced and Unannounced Inspections

The majority of inspections are carried out as announced inspections in order to ensure the presence of the relevant persons during the inspection. However, in some cases (e.g. where prior notification would jeopardise the objectives of the inspection or where the inspection needs to be carried out within a short time due to an urgent safety matter), inspections may be conducted without notification or with notification given a short time before the inspection.

2.4. Re-inspections

Re-inspections may be conducted as part of the routine inspection programme. Risk factors are assessed in order to determine the priority of re-inspections. Without being limited to the following;

When a major non-compliance was identified in the previous inspection, When the inspected party did not duly fulfil its corrective and preventive actions, When changes in the pharmacovigilance system need to be re-evaluated, In order to verify the actions taken to remedy the identified deficiency, In order to ensure the continuity of compliance with the legislation

priority is given to re-inspections.

2.5. Remote and Desk-Based Inspections

Where the locations where core pharmacovigilance activities are conducted, the safety database, and third-party service providers are not accessible at the primary inspected site, but the relevant personnel and documents are accessible, an inspection may be carried out by remote access. Under exceptional circumstances (e.g. natural disaster, pandemic outbreak or travel restrictions) and where there are logistical difficulties in conducting an on-site inspection, remote inspections may be performed. Communication tools such as the internet or telephone may be used in conducting the inspection.

Desk-based inspections are inspections conducted on documents such as the pharmacovigilance system master file, documents relating to product safety, and periodic reports.

3. PLANNING OF THE INSPECTION

When planning pharmacovigilance inspections, a systematic and risk-based approach is followed that enables the most efficient use of resources and the highest level of protection of public health. The type, frequency, scope and duration of inspections are planned accordingly. Prior to planning an inspection, the Agency may request information from the parties to be inspected.

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The factors taken into account when planning inspections are the following, without being limited thereto:

Related to the inspection: o Non-compliances identified during a previous pharmacovigilance inspection or other inspections (GCP, GMP, GDP), o Anticipation of a re-inspection as a result of the previous inspection; Related to the product: o Products subject to additional pharmacovigilance or risk minimisation activities, o Products authorised with safety-related conditions such as requiring post-marketing safety studies or additional monitoring, o Products with high sales volumes / to which a large patient population is exposed; Related to the marketing authorisation holder: o Marketing authorisation holders not previously inspected, o Marketing authorisation holders with many products on the market, o Marketing authorisation holders with no authorised product in our country previously, o Marketing authorisation holders about whom negative information and/or safety concerns have been raised by other authorities or as a result of other inspections (GCP, GMP, GDP),

o Changes in the company structure of the marketing authorization holder (such as mergers, transfers),

Regarding the pharmacovigilance system: o Delegation of pharmacovigilance activities to contracted pharmacovigilance service organizations and amendment of the contract, o Any change in the pharmacovigilance contact person since the last inspection, o Any change in the pharmacovigilance safety database, o Any change made in the pharmacovigilance center.

4. SCOPE OF THE INSPECTION

The scope of the inspection is determined according to the objectives of the inspection, the history of previous inspections, and the type of inspection. Some of the matters examined within the scope of the inspection are as follows:

ICSRs: o Collection and mutual reporting of reports; all types of ICSRs obtained from the resources of the pharmacovigilance system, from centers, from departments, from contracted pharmacovigilance service organizations carrying out pharmacovigilance duties on behalf of the marketing authorization holder, and from other departments outside drug/patient safety, o Evaluation mechanisms including the reporter's comments; evaluation of practices including the coding of adverse events according to MedDRA terminology, their seriousness, expectedness, and causality, o Follow-up and outcome records, o Reporting of ICSRs submitted to the Agency in accordance with the requirements, and information including follow-up reports for subsequent periods and reporting timelines of these reports, o Storage and archiving of ICSR records, Periodic Benefit/Risk Evaluation Reports: o Determination of preparation and submission periods, o Completeness and accuracy of the data included and the appropriateness of decisions regarding the data not included, o Format, o Submission timelines, o Handling of safety-related issues, conducting relevant analyses, and taking necessary measures, Ongoing Safety Evaluation: o Use of all sources for signal detection, o Appropriateness of analysis methods, o Appropriateness of studies and follow-up initiatives, o Fulfillment of the commitments set out in the risk management plan, o Complete and accurate submission to the Agency of requested data, o Implementation of changes in product information and safety warnings, Interventional and Non-Interventional Clinical Trials: o Reporting of suspected unexpected serious adverse reactions and reporting of non-interventional study cases,

o Collection, recording, and evaluation of cases obtained from interventional and non-interventional trials, o In special circumstances or when related to the risk management plan, submission of study results and related safety information, post-marketing safety study or post-marketing efficacy study submissions, o Appropriate selection of reference safety information, maintenance of investigator brochures and patient information relating to safety, o Inclusion of trial data in the ongoing safety evaluation, Pharmacovigilance System: o Duties, authorities, and responsibilities of pharmacovigilance contact persons, o Duties and responsibilities of the marketing authorization holder regarding the pharmacovigilance system, o

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Accuracy, integrity, and sustainability of the pharmacovigilance system master file, o Quality and adequacy of trainings, o Qualifications and experience of personnel, o Scope and processes of the quality system associated with the pharmacovigilance system, including quality control and quality assurance processes, o Suitability and purpose of computerized systems, o Explicit statement and fulfillment of pharmacovigilance responsibilities in the content of contracts and agreements with all relevant parties, Status of the system and the corrective and preventive action plan arising from previous pharmacovigilance inspection(s), Significant changes made in the pharmacovigilance system since the last inspection (e.g., change in the pharmacovigilance database, changes in the company structure such as transfers and mergers, changes in contracts, change of the pharmacovigilance contact person).

5. INSPECTION PROCESS

Pharmacovigilance inspections are carried out in compliance with the procedures related to the preparation, conduct, reporting, follow-up, and archiving of pharmacovigilance inspections.

In announced inspections, the party to be inspected is informed 1–3 weeks before the inspection date. During the preparation process for the inspection, information and documents may be requested from the parties to be inspected for review prior to the inspection.

The inspection team is determined according to the scope of the inspection, and an inspection agenda is prepared. If the inspection is to be conducted as an announced inspection, the inspection agenda is shared with the party to be inspected via e-mail prior to the inspection.

The inspection is managed through three fundamental processes: the opening meeting, the inspection, and the closing meeting. At the opening meeting, the inspection team introduces themselves and provides information about the scope and objectives of the inspection. The personnel from the inspected party participating in the inspection also introduce themselves and their companies and prepare a presentation summarizing the pharmacovigilance system. During the inspection, the name, title information, and signature of the personnel participating in the inspection are obtained.

The inspected parties shall take the necessary measures to ensure that the inspection activities are properly conducted. At the same time, they shall provide all kinds of requested information and documents

and is obliged to submit. During the inspection, the documents, operations and systems within the scope of the inspection are examined and the areas subject to the inspection are visited.

At the end of the inspection, a closing meeting is held. At the closing meeting, the deficiencies identified during the inspection are summarised by the inspection team and information about the post-inspection process is shared with the inspected party. Following each inspection, an inspection report is prepared by the inspection team. In the inspection report, the identified deficiencies are classified and it is stated whether the inspected party complies with the legislation. Inspection findings are classified as follows:

Critical (CR): Situations that adversely affect patient rights, safety or well-being within the pharmacovigilance system, its practices or processes, that carry the potential to pose a possible risk to public health, or that constitute a serious breach of the applicable relevant legislation.

Major (MA): Situations that adversely affect patient rights, safety or well-being within the pharmacovigilance system, its practices or processes, that carry the potential to pose a possible risk to public health, or that constitute a breach of the applicable relevant legislation.

Minor (MI): Situations that are not expected to adversely affect patient rights, safety or well-being within the pharmacovigilance system, its practices or processes, and public health.

Recommendation: Observations may give rise to recommendations on how to improve quality or reduce the likelihood of a deviation in the future.

The classified findings are notified in writing to the inspected party. A period of time is granted to the inspected party for remedying the deficiencies identified during the inspection, in accordance with the nature of the non-compliance.

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6. FOLLOW-UP OF INSPECTIONS

If a non-compliance is identified as a result of the inspection, follow-up is required until the corrective and preventive action plan is completed. The actions taken must be submitted to the Agency in accordance with the corrective and preventive action plan set out in Annex 1. The follow-up activities carried out are as follows:

Sharing, in writing with the inspected party, the deficiencies stated in the inspection report and granting a period of time in accordance with the nature of the non-compliance, Reviewing the corrective and preventive action plan, Re-inspection, where necessary, in order to assess whether the corrective and preventive action plan has been properly implemented, Imposing administrative sanctions if the non-compliances are not remedied within the granted period of time, Notifying the inspection outcome, where necessary, to the relevant institutions and organisations.

In the post-inspection process, provided that no non-compliance or triggering situation arises, routine pharmacovigilance inspections of marketing authorisation holders are carried out once every four years.

Marketing authorisation holders who remedy their deficiencies as a result of the inspection are required to notify the Good Pharmacovigilance Practices (GPvP/GVP) Inspection Unit, within one month, of the changes made in the matters specified, including but not limited to the following:

Changes made to the pharmacovigilance contact person and/or their deputy, A merger or demerger in the pharmacovigilance system, Change of address, Major changes made to the management and reporting of adverse drug reactions (such as database changes, transfer of services, system changes).

7. INSPECTIONS OF CONTRACTED PHARMACOVIGILANCE SERVICE ORGANISATIONS

Contracted pharmacovigilance service organisations operate on the basis of the contracted pharmacovigilance service organisation permit certificate issued following opening and renewal inspections conducted by the Agency, provided that they are found suitable. This certificate is valid for three years from the date of inspection.

Contracted pharmacovigilance service organisations are obliged to notify the Agency of major changes within one month, including but not limited to the following:

A change made to the pharmacovigilance contact person and/or their deputy, Change of address, Database change, Change in the list of procedures/instructions, A merger or demerger in the company structure, The list of companies served (notification in the format specified in Annex 2).

7.1. Opening Inspection

Opening inspections are inspections carried out where natural or legal persons wishing to operate as a contracted pharmacovigilance service organisation in our country are found suitable as a result of the assessment by the Agency of their written applications.

The documents to be submitted to the Agency during the application for an opening inspection are set out below:

The original or notarised copy of the trade registry gazette, Documents relating to the personnel who will serve as the pharmacovigilance contact person and deputy pharmacovigilance contact person: o Certificate of graduation, o Professional curriculum vitae, o Contact details valid 24 hours, o Employment commencement declaration demonstrating continuous and uninterrupted employment, o Job descriptions, Organisational chart, Document demonstrating that MedDRA terminology has been procured,

List of procedures/work instructions describing the quality system and the relevant documents, Documents relating to the computerised systems used in pharmacovigilance and documents describing the record management system.

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Provided that the documents submitted are complete, the inspection is carried out within one month.

If the deficiencies identified as a result of the opening inspection are not remedied within one year, the opening inspection application is cancelled.

7.2. Renewal Inspection

Renewal inspections are inspections conducted on the basis of a written application made to the Agency by organisations that already hold a contracted pharmacovigilance service organisation permit certificate and that indicate their wish to continue their activities six months prior to the expiry of the validity period of the permit certificate.

In the application for a renewal inspection, in addition to the documents specified for the opening inspection application, the list of companies served must be submitted. If the deficiencies identified in the renewal inspection are not remedied within the granted period(s), the application is cancelled.

A corrective and preventive action plan is submitted to the the Agency for remedying the deficiencies identified in the opening and renewal inspections. Where, as a result of the assessments made by the Agency, the applicant receives a letter of conformity demonstrating that the deficiencies have been remedied and applies for the permit certificate, a contracted pharmacovigilance service organisation permit certificate is issued.

7.3. Control Inspection

Contracted pharmacovigilance service organisations may be inspected upon complaint or ex officio where deemed necessary. The Agency has the authority to inspect contracted pharmacovigilance service organisations at any time, with or without prior notice.

As a result of the reviews and inspections conducted by the Agency; where a non-compliance is identified, a period of time is granted to the contracted pharmacovigilance service organisations for remedying the non-compliance, in accordance with its nature. Administrative sanctions are imposed on contracted pharmacovigilance service organisations that fail to remedy their deficiencies within this period.

Contracted pharmacovigilance service organisations are obliged to notify the marketing authorisation holders they serve of the deficiencies identified during the inspection. Pharmacovigilance inspections of marketing authorisation holders may also be carried out by means of control inspections.

8. REVISION HISTORY Revision No. Revision Date Rationale and Explanations 01 15.11.2022 Within the scope of the Agency's Quality System Documentation studies, the Guideline Document number has been assigned and the format has been updated.

Annex 1 Corrective and Preventive Action Plan

The responses to the inspection findings must be clear and explicit; they must contain comments addressing both the identified deficiency and the root cause of the deficiency in order to prevent it. Attention must also be paid to identifying and preventing other potential and similar deficiencies in the pharmacovigilance system.

The responses must be entered directly into the table below, and no modification must be made to the text of the finding written by the inspection team. The table specifies what must be done for the information to be entered in each field. If the requested information is not applicable to the finding in question, the expression "Not applicable" must be entered in the relevant field.

Finding

<<To be added by the inspection team>>

Root cause analysis <<To be added by the inspected party>> Identify the root causes that will prevent the recurrence of the deficiency by defining its root cause. There may be more than one root cause for each finding.

Additional assessment

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<<To be added by the inspected party>>

Assess the extent of the deficiency in the pharmacovigilance system and its potential impact on all products. Where applicable, indicate any additional assessments performed. Retrospective data analysis may be required for a complete evaluation of the data.

Corrective action(s) <<To be added by the inspected party>>

Detail the actions taken/proposed to correct the identified deficiency.

Supporting document(s) Deadline(s) <<To be added by the inspected party>> <<To be added by the inspected party>>

Preventive action(s)

<<To be added by the inspected party>>

Detail the actions taken and proposed in order to prevent the recurrence of the deficiency and its root cause. Actions for the identification and prevention of other possible similar deficiencies must also be considered.

Supporting document(s) Deadline(s) <<To be added by the inspected party>> <<To be added by the inspected party>>

Supporting document(s)

Detail the specific activities in the proposed/completed corrective and preventive action(s). For example: an updated procedure/work instruction, a record of retraining, etc. Deadline(s) Indicate the actual/proposed date(s) for the completion of each action. State when the action was completed/will be completed.

Annex 2 List for the notification of contractual pharmacovigilance service providers

REPUBLIC OF TÜRKİYE DATE MINISTRY OF HEALTH REF. NO. Turkish Medicines and Medical Devices Agency Department of Drug Inspection Good Pharmacovigilance Practices (GPvP/GVP) Inspection Unit ANKARA .....
.....

Type of service

Company name

Agreement signature date and duration

Pharmacovigilance officer

Deputy pharmacovigilance officer

Contact details of the QPPV/pharmacovigilance officers of the service provider

Contact details of the company liaison persons

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