GUIDELINE ON PHARMACOVIGILANCE INSPECTIONS

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1. INTRODUCTION

1.1. Objective and Scope

This guideline is in explanatory and guiding nature with regard to planning, conduct, reporting and follow-up of pharmacovigilance inspections in Turkey.

The objective of this guideline is to lay down procedures and principles regarding pharmacovigilance inspections performed to ensure compliance of marketing authorisation holders, contract pharmacovigilance service providers and other relevant institutions and organisations to the legislation.

The objectives of pharmacovigilance inspections are:

- To determine that marketing authorisation holders, contract pharmacovigilance service providers carrying out pharmacovigilance activities on behalf of the marketing authorisation holders, and other relevant institutions and organisations have systems, personnel, facilities and equipments in place to meet their pharmacovigilance obligations sufficiently;
- To identify, record and address non-compliance which may pose a risk to public health; and to use the inspection results as a basis for enforcement action, where considered necessary.

Marketing authorisation holders, health organisations and institutions, contract pharmacovigilance service providers and other relevant organisations should take every type of measures to carry out pharmacovigilance inspections. Their responsibilities regarding inspection are below but not limited to:

- To be always ready for inspection, and keep personnel, facility and all relevant documents used in pharmacovigilance activities ready,
- To submit every type of information and documents required in the inspection preparation process in the specified time period to the Agency,
- To submit every type of information and documents requested during the inspection to the inspection team,
- To draft corrective and preventative action plan regarding the identified findings during the inspections and overcome deficiencies in time,
- To remain compliance with legislation after inspection and notify changes made to the Agency.

1.2. Legal Basis

This Guideline has been drafted based on:

a) Point (k) of article 3 of Fundamental Law on Health Services dated 7/5/1987 No 3359,
b) Point (d) of paragraph 1 of article 352 of Presidential Decree No 1 dated 10/07/2018,
c) Points (a) and (ğ) of paragraph 1 of article 508 of Presidential Decree No 4 dated 15/07/2018,
d) Article 32 of Regulation on the Safety of Medicines dated 15/04/2014 No 28973.

1.3. Definitions

Bu kılavuzda geçen;

a) ICSR: Individual Case Safety Report
b) GCP: Good Clinical Practices,
c) GDP: Good Distribution Practices,
d) GMP: Good Manufacturing Practices
e) GPvP/GVP: Good Pharmacovigilance Practices,
f) Agency: Turkish Medicines and Medical Devices Agency,
g) MedDRA: Medical Dictionary for Regulatory Activities developed by the International Council for Harmonisation
h) CPSP: Contract Pharmacovigilance Service Providers.

2. INSPECTION TYPES

2.1. System and Product Inspections

Pharmacovigilance system inspections are designated to review the systems, procedures, personnel and facilities in place and determine their compliance of the activities with the legislation. During the inspection, product-specific examples may be used to demonstrate the operation of the system and assess the compliance.

Product related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities rather than a general system review. However, within the framework of product-related inspection, other general aspects of the system (e.g. system used for the product subject to inspection) may still be examined.

2.2. Routine and Targeted Inspections

Routine pharmacovigilance inspections are scheduled in advance and included into the inspection programme. There is no specific trigger to initiate that kind of inspections, although a risk-based approach to optimize supervisory activities is implemented. Routine inspections are usually system inspections. Particular concerns (e.g. raised by internal request or receiving complaints etc.) may also be included in the scope of a routine inspection.

Targeted inspections are initiated when a trigger is recognised. Targeted inspections may be performed to focus on specific pharmacovigilance processes or to examine identified compliance issues and their impact on a specific product. Full system inspections may be performed based on the triggers. Targeted inspections may be conducted on the occasion of one or more of the triggers listed below but not limited to:

- Benefit/risk balance of the product;
    - Benefit/risk balance is required to be examined in detail through inspection,
    - An identified risk; or delay or failure in the notification of the risk; or change in the benefit/risk balance,

    - Notification of the information including pharmacovigilance problems/concerns to the Agency,
    - Non-compliance or product safety issues identified during the monitoring of pharmacovigilance by the Agency,
    - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the Agency,
- Reporting obligations;
    - Delays or omissions in reporting,
    - Poor quality or incomplete reports,
    - Inconsistencies between reports and other information sources,
- Requests from Agency;
    - Failure to provide the requested information or data within the deadline specified by the Agency,
    - Inadequate provision of data and documents to fulfil requests for information from the Agency,
- Fulfilment of commitments;
    - Delays or failure to fulfilment of risk management plan commitments,
    - Delays or failure to carry out specific obligations relating to the monitoring of product safety,
    - Deficiencies or quality issue in reports requested as specific requirements,
- Inspections;
    - Delays in the implementation or inappropriate implementation of corrective and preventative actions,
    - Risk identification regarding product safety through other inspections (GCP, GMP and GDP),
    - Non-compliances identified through other authority inspections,
- Others;
    - Identification of non-compliances as a result of reviewing of pharmacovigilance system master file,
    - Non-inspection related information of non-compliance received from other authorities.

2.3. Announced and Unannounced Inspections

It is anticipated that the majority of inspections will be announced in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

2.4. Re-Inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritise re-inspections. In order to ensure the following factors but not limited to those, re-inspections are prioritized.

- Identification of the significant non-compliance from the previous inspection,

- Inappropriate implementation of the corrective and preventive actions by the inspected party,
- Re-evaluation of changes in the pharmacovigilance system is needed,
- To verify actions taken to correct the identified findings,
- To ensure ongoing compliance with the legislation.

2.5. Remote and Dossier Basis Inspections

Where key sites for pharmacovigilance activities, safety database, service providers are not available at the actual inspection site, but relevant staff and documents are available, remote inspections may be performed via remote access. Remote inspections may be conducted where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection.

Inspections on dossier basis are inspections conducted via reviewing pharmacovigilance system master file, documents regarding product safety, periodic reports etc.

3. INSPECTION PLANNING

Pharmacovigilance inspection planning is based on a systematic and risk-based approach to make the best use of resources whilst maintaining a high level of public health protection. The type, frequency, scope and period of inspections are determined properly. In order to plan, the Agency may request information from the parties to be inspected prior to the inspection.

Factors which are taken into consideration, when establishing pharmacovigilance inspection programmes include, but are not limited to:

- Inspection related:
  - Non-compliances identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP),
  - Re-inspection date recommended as a result of a previous inspection;
- Product related:
  - Product with additional pharmacovigilance activities or risk-minimisation activities;
  - Products authorised with conditions associated with requirement for post-authorisation safety studies or designation for additional monitoring;
  - Products with large sales volume/patient exposure.
- Marketing authorisation holder related:
  - Marketing authorisation holder that has never been subject to a pharmacovigilance inspection,
  - Marketing authorisation holder with many products on the market,
  - Marketing authorisation holder with no previous marketing authorisations in Turkey,
  - Negative information and/or safety concerns raised by other competent authorities or other inspections (GCP, GMP, GDP),
  - Changes in the marketing authorisation holder organisation, such as mergers and acquisitions,

- Pharmacovigilance system related:
    - Transfer of pharmacovigilance activities to contract pharmacovigilance service providers and changes in the contractual agreements,
    - Change of qualified person responsible for pharmacovigilance since the last inspection,
    - Changes to the pharmacovigilance safety database,
    - Changes in the sites at which pharmacovigilance activities are conducted.

4. INSPECTION SCOPE

The inspection scope is designated according to the any previous inspection history and/or inspection type. These are some of the inspected elements which are considered within the scope of the inspection;

- ICSR:
    - Collecting, receiving and exchanging reports; all types of ICSRs - from all types of sources, sites and departments within the pharmacovigilance system, including contract pharmacovigilance service providers carrying out the pharmacovigilance obligations on behalf of the marketing authorisation holder and departments other than drug/patient safety,
    - Assessment mechanisms including reporter assessments; coding of adverse events with MedDRA terminology, assessment of applications including seriousness, expectedness and causality,
    - Records of follow-up and outcome,
    - Reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting,
    - Record keeping and archiving of ICSRs,
- Periodic Benefit/Risk Evaluation Reports:
    - Identification of preparation and submitting time periods,
    - Completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included,
    - Formatting,
    - Timeliness of submissions,
    - Addressing safety topics, providing relevant analyses and actions,
- Ongoing Safety Evaluation:
    - Use of all relevant sources of information for signal detection,
    - Appropriately applied methodology concerning analysis,
    - Appropriateness of investigations and follow-up actions,
    - Implementation of the commitments stated in risk management plans,
    - Notification the data requested completely and accurately to the Agency,
    - Implementation of the changes to safety alerts and product information,
- Interventional and Non-Interventional Clinical Trials:
    - Reporting suspected unexpected serious adverse reactions and non-interventional study cases,
    - Receiving, recording and assessing cases from interventional and non-interventional trials,
    - Submission of study results and relevant safety information, where applicable, post-authorisation efficacy studies or post-authorisation efficacy studies

submissions, particularly when associated with specific obligations or risk management plan commitments,
    - Appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety,
    - The inclusion of study data in ongoing safety evaluation,
- Pharmacovigilance System:
    - The roles, competencies and responsibilities of qualified person for pharmacovigilance,
    - The roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system,
    - Accuracy, completeness and maintenance of the pharmacovigilance system master file,
    - Quality and adequacy of training,
    - Qualifications and experience of staff,
    - Coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes,
    - Fitness for purpose of computerised systems,
    - Contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to,
- Status of the system and corrective and preventive action plan(s) resulting from previous pharmacovigilance inspection(s),
- Significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in qualified person for pharmacovigilance),

5. INSPECTION PROCESS

Pharmacovigilance inspections are performed in accordance with the inspection procedures pertaining to preparing, conducting, reporting, follow-up and archiving of pharmacovigilance inspections.

With regard to announced inspections, the party to be inspected is informed a period of one to three weeks before the inspection date. During the inspection preparation, any information and/or document may be requested from the inspected party prior to inspection.

Inspection team is identified with respect to the inspection scope and inspection agenda is set up. If the inspection will be conducted as announced, inspection agenda is shared with the party to be inspected via e-mail before the inspection.

Inspection is carried out by three main processes: opening meeting, inspection and closing meeting. In the opening meeting the inspection team introduces themselves and provides information about the scope and the objectives of the inspection. Representatives participating the inspection from the inspected party also introduce themselves and present an overview of the pharmacovigilance system. During the inspection, names, titles and signatures of the participating personnel are recorded.

Inspected parties must take necessary measures to ensure that inspection activities are conducted appropriately. Also, they are obliged to provide every type of information and document requested. The documents, processes and systems to be reviewed and sites subject to inspection to be visited during an inspection will depend on the inspection scope.

At the end of the inspection, a closing meeting is held. In the closing meeting, a summary of inspection findings are presented by the inspection team and information about after inspection process is shared with the inspected party. For each inspection, an inspection report should be prepared by inspection team. In the inspection report, inspection findings are classified and whether the inspected party complies with the legislation is specified. The classification of the inspection findings are provided as follows:

- **Critical (CR):** a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.
- **Major (MA):** a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.
- **Minor (MI):** a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients
- **Recommendation:** the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Classified findings are notified to the inspected party in written. Time is granted to the inspected party according to nature of non-compliance observed during the inspection.

6. INSPECTION FOLLOW-UP

When non-compliance is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. Actions taken should be submitted to the Agency in accordance with corrective and preventive action plan in Appendix 1. The following are implemented follow-up actions:

- Sharing classified findings in the inspection with the inspected party and granting time according to nature of non-compliance,
- Review of the corrective and preventive action plan,
- Re-inspection to assess appropriate implementation of the corrective and preventive action plan,
- Administrative sanctions unless non-compliance is fixed in the timely manner,
- Communication of the inspection findings to other relevant authorities and organisations.

A marketing authorisation holder is inspected once every 4 years as long as non-compliance or trigger is not recognised.

Marketing authorisation holders who have provided compliance should notify to Good Pharmacovigilance Practices (GPvP/GVP) Department within 1 month about the changes to with regard to the following elements but not limited to:

- Change of qualified person responsible for pharmacovigilance and/or back-up person,
- Merger and separation in the pharmacovigilance system,
- Change of address,
- Major changes with regard to management and submission of reports of adverse reactions to medicinal products (changes to computerised systems used for pharmacovigilance and/or pharmacovigilance system, pharmacovigilance service delegation etc.)

7. INSPECTIONS OF CONTRACT PHARMACOVIGILANCE SERVICE PROVIDERS

Contract pharmacovigilance service providers are allowed to operate based on contract pharmacovigilance service provider license, when deemed sufficient as a result of opening and renewal inspections conducted by the Agency. This licence is valid for a period of three years from the date of inspection.

Contract pharmacovigilance service providers are obliged to notify the following elements within one month to the Agency, but not limited to:

- Change of qualified person responsible for pharmacovigilance and/or back-up person,
- Change of address,
- Changes to computerised systems used for pharmacovigilance,
- Changes in the list of procedures/instructions,
- Merger and acquisition in organisation of the company,
- List of companies to be provided service (Appendix 2 provides the format of the notification).

7.1. Opening inspection

Opening inspections are conducted when written applications of legal or natural persons willing to operate as contract pharmacovigilance service provider in Turkey are deemed sufficient as a result of evaluation by the Agency.

Documents to be submitted to the Agency whilst opening inspection application are as follows:

- The original version or a copy of the commercial registry gazette,
- Documents regarding personnel to be charged as qualified person responsible for pharmacovigilance and back-up person;
    - Graduation certificate,
    - Professional resume,
    - 24-hour available contact information,
    - Statement of employment demonstrating that the person is employed as permanently and continuously at its disposal,
    - Job descriptions,
- Organisational structure,

- Document demonstrating that MedDRA terminology has been obtained,
- List and documents of procedures/instructions explaining quality system,
- Documents regarding computerised systems used in pharmacovigilance and documents explaining record management system.

Opening inspection is conducted within one month, if the submitted documents are complete.

If the findings identified during opening inspection are not fixed within one year, opening inspection application shall be cancelled.

7.2. Renewal Inspection

Renewal inspections are conducted based on written application submitted by providers already owning contract pharmacovigilance service provider license and stating that they are seeking to continue their activities six months before the expiry of the validity period.

In addition to the requested documents for opening inspection, the list of companies to be provided service should be submitted for renewal inspections. If the findings identified during renewal inspection are not fixed within the granted time period(s), the application shall be cancelled.

Corrective and preventative action plan to address findings identified during opening inspection or renewal inspection should be submitted to the Agency. Provided that the applicant receiving compliance letter demonstrating that the findings have been corrected, contract pharmacovigilance service provider license may be issued, if the applicant is to apply for the licence.

7.3. Control Inspection

Contract pharmacovigilance service providers may be inspected directly or upon complaints. The Agency has authorisation to inspect contract pharmacovigilance service providers at any time as announced or unannounced.

In the event of non-compliance as a result of examinations and/or inspections, time is granted to contract pharmacovigilance service providers according to nature of the identified non-compliances. Regulatory sanctions are imposed on CPSPs which do not correct non-compliances in the stated time period.

Contract pharmacovigilance service providers are obliged to notify the identified findings during regulatory inspections to marketing authorisation holders which they provide service. Pharmacovigilance inspections of marketing authorisation may be performed whilst control inspections of CPSPs.

Appendix 1 Corrective and preventative action plan

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered into the table(s) below, without changes to the inspector team's text that describes the findings. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Finding
<<inspection team to add text>>
Root cause analysis
<< inspected party to add text >> Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further assessment
<<inspected party to add text >> Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective action(s)
<< inspected party to add text >> Detail the action(s) taken / proposed to correct the identified deficiency.

Deliverable(s)	**Due date(s)**
<< inspected party to add text >>	<< inspected party to add text >>

Preventative action (s)
<< inspected party to add text >> Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.

Deliverable(s)	**Due date(s)**
<< inspected party to add text >>	<< inspected party to add text >>

Deliverable(s)
Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due date(s)
Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Appendix 2 List for Notification of Contract Pharmacovigilance Service Providers

Republic of Turkey DATE
Ministry of Health NO
Turkish Medicines and Medical Devices Agency
Department of Medicine Inspection
Good Pharmacovigilance Practices (GPvP/GVP) Inspection Unit
ANKARA

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Service type	Company name	Date of signing contract and duration	Qualified Person responsible for pharmacovigilance	Back-up Person responsible for pharmacovigilance	Contact information of CPSP representatives	Contact information of company contact persons