Guidelines for Conducting Pharmacovigilance Inspections

1. Purpose

To monitor compliance of registration/authorization holders with their obligations in connection with pharmacovigilance and drug safety, the Ministry may undertake direct inspection of pharmacovigilance systems in accordance with the applicable regulatory requirements.

These inspections are aimed at evaluating the practices of the registration/authorization holder and/or the contract pharmacovigilance service provider for pharmacovigilance data management and the relevant systems.

These inspections may be conducted at a single site or several sites. The inspections may be routine or in response to specific concerns.

During routine inspections, and depending on the scope of the inspection, the inspectors examine whether the pharmacovigilance system, implemented and submitted to the Ministry by the registration/authorization holder, has been accurately represented.

Additionally, any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the registration/authorization holder may be inspected, in order to confirm their capability to support the registration/authorization holder's compliance with pharmacovigilance obligations.

This guideline provides an outline of the minimum requirements that may be applied to ensure achievement of pharmacovigilance inspection goals.

2. Responsibilities

The inspectors are under obligation to ensure that any pharmacovigilance inspections conducted on behalf of the Ministry are performed in accordance with this Guideline and currently applicable regulations.

3. Inspection Types

3.1 Routine Inspections

Routine inspections may be conducted in the intervals set by the Ministry.

3.2 Targeted Inspections

Targeted inspections may be performed when one or more of the following arise:

- Triggers for the inspection are identified which do not relate to specific concerns about a product's safety or actual non-compliance, e.g.:
    - The registration/authorization holder has not previously been inspected
    - The registration/authorization holder has placed his first product on the market
    - The registration/authorization holder has recently undergone a merger or takeover process
    - The registration/authorization holder has changed his system significantly (e.g., established a new database system, contracted out reporting activities to a contract pharmacovigilance service provider).
- Significant issues indicated below, relating to specific concerns about a product's safety or actual non-compliance, require an inspection:

- Delays in carrying our or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of marketing authorization.
- Delays in expedited or periodic reporting.
- Incomplete reporting.
- Submission of poor quality or incomplete Periodic Safety Update Reports (PSUR).
- Inconsistencies between reports and other information sources.
- A change in the risk-benefit balance of the products, or failing to report such changes.
- Previous inspection experience of the inspectors.
- Company information received from other authorities.
- Poor or delayed follow-up to requests for information from the Ministry.
- Communication of information to the general public on pharmacovigilance concerns which concern the society in general, without giving prior or simultaneous notification to the Ministry.
- Product withdrawal without notifying, or adequately notifying, the Ministry.

3.3 Pharmacovigilance System Inspection

These inspections are designed to review the suitability of the systems, personnel, and the physical environment, as well as their compliance with pharmacovigilance obligations. Product may be used as example during these inspections to test the system. These inspections may be routine or targeted.

3.4 Product-Specific Inspections

These inspections focus specifically on a given product and are usually targeted as a result of triggers that have been identified.

3.5 Inspection of Contract Pharmacovigilance Service Providers

Any contract pharmacovigilance service provider, carrying out pharmacovigilance activities in whole or in part on behalf of, or in conjunction with, the registration/authorization holder, may be inspected in order to confirm their capability to support the registration/authorization holder's compliance with pharmacovigilance obligations.

3.6 Unannounced Inspections

Inspections may be conducted with or without advance notice.

4. Preparation for a Pharmacovigilance Inspection

The goals of a pharmacovigilance inspection will vary depending on the criteria to be applied during the inspection.

The scope of the inspection will depend on the nature of the inspection (routine/triggered) and on the requirements of the inspection request.

Preparatory work for a pharmacovigilance inspection should involve collaboration of the inspectors commissioned for conducting the inspection with the relevant departments as necessary. The preparatory work should also involve the assessors of a particular product or other specialist (e.g., "Information Technology" specialists, depending on the scope of the inspection). These experts may also be included on the team when forming the inspection team.

An inspection plan should be prepared in line with the scope and objectives of the inspection.

The registration/authorization holders and/or their contract pharmacovigilance service provider may be outsourcing all or a part of their pharmacovigilance and safety assessment obligations. It is important to ascertain from the "Pharmacovigilance System Overview (PSO)", or by obtaining additional information, organizational charts, contracts/agreements and standard operating procedures (SOP), as to how the pharmacovigilance responsibilities are divided both within the company and with other stakeholders.

It is equally important to ascertain where the required information resides when planning the pharmacovigilance inspection. Several sites/departments may need to be visited in order to obtain a complete view of the pharmacovigilance system of the registration/authorization holder.

Access to the global pharmacovigilance database, and provision by the registration/authorization holder of the resources needed to perform searches on this database should be agreed in advance with the registration/authorization holder, prior to the inspection.

Prior to the inspection, it should be checked whether any significant changes have been made to the system that would have an impact on the inspection plan.

The data and documentation review that should be performed as part of the pharmacovigilance inspection by general sampling or with respect to a particular product or therapeutic area should be agreed prior to the inspection, and should be compatible with the scope and objectives of the inspection. Additional data and documentation for review may also be identified during the inspection. An adequate sample of data and documentation to undergo review should be formed, and may be requested to be provided to the inspector(s), as part of the preparatory work.

The sample size may be decided taking into account the following factors:

- The organization of the registration/authorization holder and the distribution of the pharmacovigilance and safety evaluation tasks.
- The number of products granted registration/authorization.
- The types of products and therapeutic areas.
- The specific concerns that need to be addressed during the inspection.
- The clinical trials and pharmacoepidemiological studies conducted by the registration/authorization holder.
- Potential different origins of the reports.
- Issues of non-compliance identified during previous inspections.

The sample should give a good representation of the registration/authorization holder's conduct of pharmacovigilance.

If necessary, the Ministry may require the registration/authorization holder to provide a "Pharmacovigilance System Overview (PSO)", outlining the pharmacovigilance system in the format described in the appendix, in order to facilitate the planning and preparatory work. The PSO should be clear and concise, if possible no longer than twenty five pages excluding appendices. The PSO should be submitted in both hardcopy and electronic form. The expression "not applicable" should be inserted in appropriate sections of the PSO which are inapplicable to the registration/authorization holder. Where the company has in place a single pharmacovigilance system notwithstanding the origin of adverse reactions, it is appropriate to issue a single PSO. Where different pharmacovigilance

systems are employed by the company, several PSOs will have to be issued, which may result in several inspections of the same registration holder to inspect his individual systems.

Any requests for data and documentation should be made in a timely manner in order to allow the inspectee(s) to provide all the requested documents for review by the inspection team.

5. Conduct of a Pharmacovigilance Inspection

5.1 Opening Meeting

Before the start of the inspection, an opening meeting must take place between the inspector(s) and in particular the key personnel of the inspectee(s), for the purpose of providing an overview of the inspection plan. In particular, the following points should be addressed during the opening meeting:

- The lead inspector should describe the purpose and the scope of the inspection.
- The lead inspector should outline the Regulations and Guidelines that provide the basis for the inspection, and briefly describe the methods to be used during the conduct of the inspection.
- The item headings in the Pharmacovigilance Inspection Plan should be mutually agreed, and inspection logistics should be discussed.
- The lead inspector should re-confirm that the resources, documents and means required by the inspectors are available.
- The time and date for the closing meeting and any interim meetings should be confirmed.
- Appropriate personnel should provide general information about the registration/authorization holder and/or contract pharmacovigilance service provider. The general information will also include an overview of the organization and other stakeholders relevant to drug safety, the systems used for the collection, collation, evaluation and reporting of adverse drug reactions, a summary of significant changes, if any, since the previous inspection, and a summary of significant changes that are planned for the future.

5.2 Conduct of the Inspection/Collecting Information and Recording Observations

Full details of the inspection activities should be provided in the inspection plan. Nevertheless, during the inspection, the inspector(s) may amend the plan to ensure that the inspection objectives are achieved.

Sufficient information to fulfill the inspection objective(s) should be collected through examination of relevant documents and computer systems, as well as through the conduct of interviews with relevant personnel.

If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has a legal right of access, these refusals should be documented and included in the inspection observations.

At least the following items should be reviewed as part of the pharmacovigilance inspection:

5.2.1 Legal and Administrative Aspects

- Documentation of the responsible parties for pharmacovigilance/drug safety activities.
- Documentation of the selection and appointment of the registration/authorization holder’s qualified person for product safety.

- Records of information on all suspected adverse reactions.
- Contracts for the services outsourced by the registration/authorization holder.
- Whether the adverse reaction reports have been submitted on time, in accordance with the applicable regulatory provisions.
- Preparation and submission of annual safety reports/summary of product characteristics (including revisions), clinical trial brochures (including revisions), and periodic safety update reports, including discussion relating to off-label use/pediatric use.
- Collection and reporting of serious adverse reactions in clinical trials.
- Collection and reporting of spontaneous adverse reactions.
- Collection, follow-up and reporting of pregnancy exposure.
- Collection, follow-up and reporting of the effects on the pediatric population.
- Provision to the ministry of any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly any information concerning post-authorization safety studies (including studies included in risk management plans and pediatric investigation plans).

5.2.2 Organizational Structure

5.2.2.1 Quality System and Standard Operating Procedures (SOP) for Pharmacovigilance Activities

- SOPs should be documented to cover all aspects of pharmacovigilance/drug safety. These SOPs should at least include the following:
    - Collection and management of all pharmacovigilance data (from healthcare professionals, quality complaint departments, regulatory affairs departments, etc.) and of serious adverse reaction data:
        - Causality assessment.
        - Determination of seriousness and listedness/expectedness and whether adverse reactions reports are expedited.
        - Coding.
        - Avoidance of duplicate reporting.
        - Ensuring compliance with reporting requirements.
        - Identifying and tracking initial and follow-up reports.
        - Ensuring an adequate and complete follow-up.
        - Arranging inter-organizational exchange of reports.
        - Ensuring completeness of the information contained in databases.
    - Review, validation and follow-up of suspected adverse reactions.
    - Data management (accurate storage and accessibility of information, tracking of reports and ensuring timeliness of submissions, compliance with confidentiality requirements).
    - Expedited reporting to the Ministry, and, where necessary, to all relevant units.
    - Monitoring of worldwide scientific literature.
    - Collation and submission of periodic safety update reports/annual safety reports.
    - Management of requests for information by the Ministry.
    - Management of urgent safety restrictions and type II variations.

    - Updating of core safety information/developing safety information/summary of product characteristics (including relevant results of pediatric studies).
    - Signal detection/trend analysis activities.
    - Management of communications with the Ministry as necessary.
    - Creating the risk management plans.
- Organizational charts to identify the key personnel.
- Control of all the documentation, including writing, review, approval, updating, distribution and implementation of SOPs.
- Review of quality control processes and documentation.
- Review of corrective and preventive action processes and documentation.
- Control of the pharmacovigilance system:
    - Determining whether controls of pharmacovigilance/drug safety activities have been performed, and identifying the organization who is in charge of this functions.
    - The processes for communicating and addressing control findings.
    - Controls of external institutions/organizations, if any, whose services have been hired.
    - Qualification and training of controllers.

5.2.2.2 Qualified Person for Product Safety

- Documentation identifying the qualified person for product safety, along with qualification and training documentation.
- Documentation of the qualified person for product safety and contact details in the quality system
- Verification that the qualified person for product safety has adequate (direct, timely) access to all relevant pharmacovigilance/drug safety information.
- Verification that the same qualified person for product safety has been notified to all relevant competent authorities.
- Verification that the qualified person for product safety has sufficient authority within the company to make amendments to the pharmacovigilance system in order to ensure compliance.
- Appointment documentation.
- Documentation that the person who deputized for the qualified person for product safety in his absence had been appointed as a deputy and so notified to the Ministry, and verification that this procedure will be applied.

5.2.2.3 Resources and Training of Personnel

- Interview of personnel involved in any pharmacovigilance activity.
- Documentation of job description, qualifications and training of individuals involved in any stage of pharmacovigilance/safety evaluation process.
- Documentation on policies and procedures for training of personnel.
- Allocation of deputies to key personnel.

5.2.3 Equipment and Computer Systems

- Computer systems in use (administration, use and hardware/software specifications and validation approvals).
- Migration of data and legacy system, where relevant.
- System for the archiving and retrieval of documents.

- Procedure for collecting, archiving, filing and recovering documents.
- Controlled access to the archives.

5.2.4 Safety Information from Clinical Trials

Safety information in connection with clinical trials undertaken by the registration/authorization holder and matters relating to the harmonization of pharmacovigilance databases may be inspected in accordance with the applicable guidelines.

5.2.5 Safety Information from Other Departments

The minimum topics that should be considered when evaluating safety information received from other departments, including quality defects, medicinal or legal information, are the following:

- Quality defects and complaints should be examined to determine whether there are quality defects that could lead to adverse reactions or whether there may be a quality defect reported that could be the cause of actual or potential adverse reactions and vice versa. Reconciliation of these data should be arranged.
- Handling of medical information and legal information should also consider detection of potential adverse reactions.
- Information collected by marketing and regulatory affairs departments.

5.2.6 Data/Documentation Review

The strategies used during inspection will depend on the objective(s) of the inspection, and the minimum elements that must be considered during review of data/documents are provided below:

- Confirmation that potential adverse reactions from any source have been processed appropriately.
- Determination of seriousness.
- Determination of expectedness.
- Causality assessment.
- Consistency and correctness of coding with terminologies used/internal procedures.
- Quality and completeness of the medical review.
- Quality of the information included in case summaries.
- Adequacy of follow-up measures taken.
- Adequacy of follow-up information collection and reporting.
- Any specific questions raised in the inspection request.
- Timely submission of expedited and periodic reports to authorities.
- Have all relevant cases (all serious adverse reactions and all non-serious, unlisted spontaneously reported adverse reactions) been examined or included in the line listings of the periodic safety update report covering the relevant time period?
- Have qualified, serious reports from clinical trials been reported in an expedited manner and included in periodic safety update reports and annual safety reports?
- Have specific requests in the assessment reports e.g. for the presentation and submission of data, been appropriately addressed?
- Can serious adverse reactions/adverse events be identified in the listings of non-serious adverse reactions/adverse events?
- Have the results from literature searches been appropriately reviewed?

- Can specific literature cases be accessed in the database?
- Have new safety issues arising from post-approval studies, conducted worldwide, been reported promptly to competent authorities?
- Adequacy of quality control process and follow-up measures taken (corrective action process).

5.2.7 Recording Inspection Observations.

All inspection observations should be documented. If possible, copies should be made of records containing inconsistencies or illustrating non-compliance.

At the end of the inspection, the inspectors should list and review the non-compliances or system deficiencies. The inspector(s) should ensure that these are documented in a clear and concise manner and are supported by objective evidence. All reported observations (findings) should be indicated, taking into account the specific requirements of the regulations or other related documents based on which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organization should be documented.

5.2.8 Closing Meeting

At the end of the inspection, the inspector(s) should conduct a closing meeting with the inspectee. The qualified person for product safety, his deputy or other responsible persons for pharmacovigilance activities should attend the meeting. The purpose of the closing meeting is:

- To summarize inspection findings and observations to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspectors or the inspectees;
- To provide the inspectee with an opportunity to correct any misconceptions made by the inspector or to supply additional information in response to the findings;
- To clarify the procedures for the distribution of the inspection report, for the production of responses to the inspection report and for inspection follow-up (as appropriate);
- To request copies of any documents that may be required by the inspector (e.g. to assist with the preparation for other activities associated with the inspection).

An inspection may consist of visits to more than one location. If possible, a closing meeting may be held at each location inspected.

6. Preparation of Inspection Report

The lead inspector, in agreement with other inspectors on the team, shall prepare an inspection report in accordance with the appropriate guideline.

7. Classification of Inspection Findings

1. **Critical:** a situation 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.
2. **Major:** a situation 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 violation of applicable legislation.

3. **Minor:** a situation in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

8. Follow-up of Inspection Findings

Where an inspection reveals non-compliances, the registration/authorization holder will be required to prepare an action plan, containing solution proposals to correct the non-compliances and to avoid their recurrence. The registration/authorization holder may be required to provide report(s), containing evidence of the progress and completion of the action plan. There may be a follow-up inspection at an appropriate time to verify the progress and success of the action plan containing the solution proposals.

9. Regulatory Action and Sanctions

In the event of non-compliances revealed during an inspection, the regulatory action that may be taken include:

- Education and facilitations: The registration/authorization holder is informed of the non-compliance and advised on how this can be remedied.
- Inspection: Non-compliant registration/authorization holders may be re-inspected to determine whether the non-compliance has been remedied.
- Warning: The Ministry may issue a formal warning to the registration/authorization holder, reminding him of his pharmacovigilance regulatory obligations.
- Naming registration/authorization holders: The Ministry may make public a list of registration/authorization holders who are seriously or persistently non-compliant.
- Urgent safety restriction: The Ministry will act in accordance with the applicable legislation.
- Variation of Registration: The Ministry will act in accordance with the applicable legislation.
- Suspension of Registration: The Ministry will act in accordance with the applicable legislation.
- Revocation of Registration: The Ministry will act in accordance with the applicable legislation.

Appendix – 1: Pharmacovigilance System Overview

1. Contact Details

   1.1. Registration/Authorization Holder's
      1.1.1. Name
      1.1.2. Address
      1.1.3. Telephone numbers
      1.1.4. Network address
   1.2. Qualified Person for Product Safety
      1.2.1. Name and other functions
      1.2.2. Address of place of work
   1.3. Location where pharmacovigilance activities are conducted
   1.4. Number of products registered/authorized, number of registrations/authorizations held in the country

2. Company Organization and Pharmacovigilance Model

   2.1. Brief company profile including the following:
      - Company's affiliates/worldwide locations.
      - A list of products in which the company is specialized and its therapeutic area(s) (products registered/authorized and products for which a registration/authorization application has been submitted).
      - Consolidations or mergers in recent years (and their impact on and relevance to pharmacovigilance).

   2.2. An overview of the conduct of pharmacovigilance activities within the company.

3. Pharmacovigilance System

   3.1. An overview of the pharmacovigilance activities conducted at the pharmacovigilance units in Turkey and worldwide, if any.

   This section should be completed by providing an overview of compliance with applicable Regulations and Guidelines, and should incorporate the following sections:

      - An overview of pharmacovigilance activities conducted by other units with overlapping pharmacovigilance functions (e.g., medical, regulatory affairs, or quality control departments).
      - Handling of spontaneous adverse reaction reporting (review of data starting from the time of receipt, and expedited reporting. Flow diagrams may be used.)
      - A detailed description of the compliance monitoring activities performed.
      - How are the Periodic Safety Update Reports (PSURs) and National Reports prepared, and what is their submission procedure to the Ministry?
      - A list of routine functions of the qualified person for product safety.
      - A description of the signal generation and summary of product characteristics (SmPC) modification procedures.
      - Risk management plans (RMP) (Is there an RMP that the company has for any of its products?)

4. Computerized Systems for Pharmacovigilance

   4.1. A detailed description of the data processing systems/databases used to collect, compare, and evaluate suspected adverse reactions (e.g., spontaneous reports).
   4.2. A detailed description of the computerized systems used in the country to collect/monitor adverse reaction reports, including databases used for medical information consultancy (diagrams may be used to illustrate the interaction between the systems).
   4.3. A summary of the databases used to collect, compare, and evaluate suspected adverse reactions reported in the past five years (if any).

5. Quality Control System

5.1. Is it the company's intention to maintain the pharmacovigilance system intact during the six months after completion of the PSO? If not, a summary of the planned modifications should be provided.

5.2. Who is responsible for examining the company's pharmacovigilance system? For how long and where are the examination reports kept?

6. Training Records

6.1. A description of the training record system, including job description, biographies, and training records of key pharmacovigilance personnel.

7. Archiving

7.1. A brief description of the archiving activities of pharmacovigilance documents.

7.2. If a service provider has been retained on contract to safeguard the pharmacovigilance documents, the name and address of the archive location.

8. Any questions and/or remarks relating to the information submitted by the company and/or requested by the Ministry

9. Appendices

9.1. All appendices should be enumerated.

9.2. Each page should have a header/footer containing the company name, the number and title of the appendix , and the page number.

9.3. If appendices cannot be prepared, the reason(s) therefor should be described under item 8.

9.4. The following aspects should be appended to the PSO as a supplement:

9.4.1. Key Personnel

9.4.1.1. The names and titles of persons assigned to pharmacovigilance functions in Turkey, and the organizational chart.

9.4.1.2. Updated biographies and job descriptions of the qualified person for product safety and his deputy.

9.4.1.3. The names and titles of persons responsible for providing medical information, or of persons to whom these functions have been delegated, and their organizational charts.

9.4.2. All Company Products

9.4.2.1. A list of all of the company's products which are registered/authorized in Turkey (the active substance(s), whether it is marketed in the country, and its commercial name in Turkey should be indicated for individual products).

9.4.2.2. The top five products in respect of which the highest number of adverse reactions have been reported during the year preceding the completion of the PSO.

9.4.3. Quality Control System

9.4.3.1. Standard operating procedures of pharmacovigilance and other relevant units (e.g., medical, regulatory affairs, or quality control departments) in matters related to pharmacovigilance.

9.4.4. Reporting to the Ministry and Statistics

9.4.4.1. Whether the expedited reporting requirements have been met for spontaneous reports received by the Ministry.

9.4.4.1.1. The following data for each month from the past two years should be submitted:

- Total number of serious and non-serious adverse reaction reports by the company.
- Total number of adverse reaction reports submitted to the Ministry according to the expedited procedure.
- Total number of reports submitted late to the Ministry.
- Ratio of number of cases reported late to the total number of reports submitted.

9.4.4.2. Compliance with the PSUR/NR submission deadlines which must be submitted after sixty days from the data-lock point.

9.4.4.2.1. The following data should be submitted for the PSURs/NRs submitted to the Ministry in the past two years:

- Product name.
- Data-lock point.
- Date of submission to the Ministry (if no PSURs have been submitted to the Ministry in the past two years, data from the past five years should be entered, ordered by date).

9.4.5. Third Party Agreements (e.g., with service providers rendering medical information or pharmacovigilance services).

9.4.5.1. Any details regarding outsourcing of any function or activity, directly or indirectly related to pharmacovigilance, within the country to a party other than the registration/authorization holder.

9.4.6. Product Safety Issues

9.4.6.1. A list of the products withdrawn worldwide for safety concerns during the past five years (date, country where withdrawn, reason).

9.4.6.2. Details of urgent safety restrictions implemented in the past two years by the registration/authorization holder or by competent authorities.

9.4.7. Other

9.4.7.1. Documents in connection with the following activities should be submitted:

- Processing of spontaneous adverse reaction reports.
- Follow-up of individual cases.
- Expedited reporting procedure to the Ministry.
- Monitoring compliance with the 15-day periods.
- Preparation and submission of PSURs/national reports.
- Signal analysis.
- Responding to medical inquiries.