FOOD AND DRUGS AUTHORITY

GUIDELINES FOR CONDUCTING PHARMACOVIGILANCE INSPECTIONS

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1.0. INTRODUCTION

To ensure that Local Representatives and Manufacturers comply with pharmacovigilance regulatory obligations and to facilitate compliance, the Food and Drugs Authority shall conduct Pharmacovigilance inspections of the companies whose products have been granted marketing authorization. Inspections will be routine as well as unannounced to the Local representatives suspected of being non-compliant. The results will be used to help the Local representatives and Manufacturers improve compliance and may also be used as a basis for regulatory action. The scheduling and conduct of these inspections will be driven by routine programmes and by risk analysis criteria.

2.0. GLOSSARY

In these guidelines, unless the context otherwise states: -

"Authority" means the Food and Drugs Authority

"Risk Management Plan" A systematic approach and set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to products, and the assessment of effectiveness of those interventions and how these risk will be communicated to the Authority and the general population.

"Local Representative"

The company or legal entity who represents the MAH in Ghana and perform functions delegated by the MAH.

"Local Distributor or Local Agent"

A company or legal entity appointed by the manufacturer or the Marketing Authorization Holder to import, receive as donation, distribute or sell a medicinal product in Ghana.

"Marketing Authorization Holder"

Marketing Authorization Holder: The company or legal entity in whose name the marketing authorization for a product has been granted and is responsible for all aspects of the product and compliance with the conditions of marketing authorization.

"Pharmacovigilance System Master File"

A document which describes the pharmacovigilance system for one or more products of the marketing authorization holder.

"Qualified Person for Pharmacovigilance (QPPV)" An individual named by a Marketing Authorization Holder (MAH) as the main person responsible for ensuring that the company (the MAH) meets its legal obligations under the Public Health Act, 2012, Act 851, Section 125 for monitoring of the safety of the product marketed in Ghana.

3.0. REQUIREMENTS

3.1. General Requirements

3.1.1. Pharmacovigilance Inspections

To ensure that Local representatives and Marketing Authorization Holders (MAH)comply with pharmacovigilance regulatory requirements and to facilitate compliance, the Authority shall conduct Pharmacovigilance inspections.

Inspections will be routine as well as targeted to Local representatives and Marketing Authorization Holders suspected of being non-compliant. The results will be used to help Local representatives and Manufacturers improve compliance and may also be used as a basis for enforcement of regulatory action.

The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.

The inspection will be conducted where pharmacovigilance activities of the Local representative or Marketing Authorization Holders are located.

3.1.2 Objectives of Pharmacovigilance Inspections

- Improve pharmacovigilance system established by Local Representatives and MAHs
- Ensure compliance with the pharmacovigilance obligations by the Local representative and MAH in order to protect public health and safety
- Enforce regulatory requirements

3.1.2. Types of Pharmacovigilance Inspections

3.1.2.1. Routine Inspections

These are scheduled inspections that Local representatives or MAHs shall undergo at periods as determined by the Authority. The frequency of routine inspection will be determined on the basis of risk analysis criteria.

Local representatives or MAHs shall be given advanced notices of these inspections. These inspections shall be aimed at identifying whether the Local representatives or MAHs have the personnel, systems and facilities in place to meet their regulatory obligations for registered products under the Public Health Act 2012.

These inspections may be requested with one or more specific products selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the Local representatives or MAHs and their compliance with their regulatory obligations.

3.1.2.2. Unannounced Inspections

These are ad hoc inspections that are triggered as a result of, for example, safety issues, suspected violations of legislation relating to the monitoring of the safety of products. Under these circumstances the Local representatives or MAH will not be notified of these inspections in advance.

3.2. Specific Requirements

3.2.1. The Inspection Schedule

The Authority will carry out pharmacovigilance inspection for Local Representatives and MAHs based on risk analysis.

This will help to focus resources to improve the protection of public health where there is a potentially higher risk.

Factors which may affect inspection scheduling may include but not limited to the following:

3.2.1.1. number of products issued marketing authorization by the Authority;

3.2.1.2. product portfolio;

3.2.1.3. failure to provide details of the Qualified Person for Pharmacovigilance to the Authority;

3.2.1.4. number of products with known safety risks;

3.2.1.5. non-compliance with the Authority's reporting requirements

3.2.2. Phases of the Inspection Process

There are three main phases of each pharmacovigilance inspection:

Planning: A preliminary notification to the Local representative or the MAH about the scheduled inspection and pertinent documents to facilitate the inspection may be requested by the Authority at least 14 days to the scheduled inspection date. The date for the inspection is agreed together with the Local representative or the MAH.

The Authority may request for the following documents prior to the inspection. This may include but not limited to;

3.2.2.1. Pharmacovigilance System Master File (PSMF) to reflect Ghanaian Pharmacovigilance system including but not limited to human resource for pharmacovigilance, organizational chart for pharmacovigilance, job description of the QPPV and other staff involved in pharmacovigilance, information relating to the QPPV, SOPs and other work instructions. *For details refer to* ***Appendix. I.***

3.2.2.2. Minutes of meetings specific to pharmacovigilance

3.2.2.3. Individual adverse reaction cases files and CIOMS reports;

3.2.2.4. Recent PSURs / PBRERs for marketed products;

3.2.2.5. Ghana specific RMPs for selected products when applicable;

3.2.2.6. line listings of adverse reaction reports;

Conduct of Inspection: The inspection may be conducted at the Local representative or the MAH's location, and if a third party is involved in any pharmacovigilance activity, their site may also be inspected by the Authority. The inspection will normally commence with an opening meeting and end with a closing meeting. The Local representative or the MAH has the right to choose which members of staff participates in these meetings but shall include the QPPV.

Reporting and Follow-Up: Deficiencies found during the Authority's pharmacovigilance inspections are graded as follows.

***Critical*:** 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 Public Health Act, 2012 and applicable Food and Drugs Authority guidelines.

***Major*:** 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 Public Health Act, 2012 and applicable Food and Drugs Authority guidelines

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

In general, preliminary findings will be communicated at the closing meeting. An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report. The report is sent to the Local representative or MAH, usually within 30 working days of the site visit or the date of the provision of the last document requested. It should be noted that the factual matter contained in the inspection report relates only to those things that the inspection team sees and hears during the inspection process.

3.2.3 Responding to Findings

Following the issue of the inspection report, the Local representative or MAH is requested to respond to any deficiencies identified and to provide the Authority with an appropriate corrective action and preventative action plan (CAPA) within 21 working days or a deadline to be determined by the Authority based on the magnitude of non-compliance identified.

The Local representative or MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

Note that, in some circumstances, the Local representative or MAH may be required to take immediate action to address a critical or major finding, for the protection of public health and safety.

3.2.4 Record Management and Archiving

All pharmacovigilance data should be maintained in a secure area (dedicated for that purpose) and the data should be stored to ensure:

- Limited access to data
- Protection of confidentiality of patients
- Protection of information
- Easy retrieval

Documents must be stored in secured cabinets that will protect them from hazards (rodents, flood, fire)

Pharmacovigilance data should be stored throughout the life cycle of the product.

4.0. SANCTIONS

The following regulatory sanctions shall be applied in the case of non-compliance;

4.1 Local representative or Manufacturer may be informed of non-compliance and advised on how this can be remedied.

4.2 Non-compliant Local representative or Manufacturer may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.

4.3 Warning; The Authority may issue a formal warning reminding Local representative or Manufacturer of their pharmacovigilance regulatory obligations.

4.4 Black listing non-compliant Local representative or Manufacturer

4.5 Product recalls e.g. where important safety warnings have been omitted from product information;

4.6 Deferral of application for registration of product(s) until corrective and preventive actions have been implemented;

4.7 The Authority may consider making public a list of Local representative or Manufacturer found to be seriously or persistently non-compliant.

4.8 Urgent Safety Restriction

4.9 Variation of the Marketing Authorization

4.10 Suspension of the Marketing Authorization

4.11 Revocation of the Marketing Authorization

5.0 PENALTIES

Non-adherence to the requirements of these guidelines by Local Representatives Marketing Authorization Holders and Marketing Authorization Holders will result in Authority imposing sanctions as prescribed by the Public Health Act, 2012, Act 851, Section 142 and Section 148, Subsections 4 and 5.

APPENDIX I: Format for the Pharmacovigilance System Master File

Cover page

The name of the MAH or Local Representative

The date of preparation and last update

Section I: Administrative Information

A signed statement that the Local Representative or the Marketing Authorization Holder (MAH) has the necessary means to fulfill the tasks and responsibilities listed in the underlisted references;

- Section 125 of the Public Health Act, 851, 2012
- Guidelines for Qualified Person for Pharmacovigilance (Section 3.2)
- Guidelines for Reporting Adverse Reaction (Section 3.2.1)
- Guidelines for Conducting Pharmacovigilance Inspections
- Guidelines for Safety Monitoring of Medicinal Products

Section II: The QPPV

The details of the Qualified Person for Pharmacovigilance (QPPV), i.e. name and contact details [address, telephone number, fax number, email)

The CV (curriculum vitae) of the QPPV

The job descriptions of the QPPV

The proof that the QPPV has attended the prescribed training programme approved by the FDA and other training programmes

The proof that the QPPV has been officially designated

Back-up procedure to apply in the absence of the QPPV and the training provided for the back-up

A signed contract between the Local Representative or the MAH and the QPPV

The list of tasks that has been delegated by the QPPV and to whom these have been delegated

Section III: The organizational structure of the MAH

The description of the organizational structure of the Local Representative or the MAH relevant to pharmacovigilance showing the position of the QPPV in the organization

Diagrams showing the organizational charts will be helpful and preferred

Any pharmacovigilance related activities performed by third parties

Description of co-marketing agreements and contracts of pharmacovigilance activities, if any.

List of product(s) for which the QPPV is responsible

Section IV: Sources of Safety Data

Inflow of adverse reaction reports and safety information

Description of the stages involved in the processing of ICSRs including the timelines for submission to regulatory authorities including the Food and Drugs Authorities

Outflow of safety data to regulatory authorities including the Food and Drugs Authorities

List of the sources of safety data, including but not limited to spontaneous reports, study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorization holder

Section V: Computerized systems and databases

Description of the functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose

Responsibility for the operation of the database and training provided for the type of training to be provided to staff(s) involved the database operations

Validation, maintenance, backup and access controlled

Management of the data for paper-based systems should be described and mechanisms used to assure the integrity and accessibility of the safety data and in particular the collation of information about adverse drug reactions.

Section VI: Pharmacovigilance processes

The list of standard operating procedures

Details of all the current standard operating procedures relating to pharmacovigilance which are expected includes but not limited to the following;

1. Archiving and retrieval
2. Corrective and Preventive Action (CAPA) processes for pharmacovigilance
3. Causality assessment, if applicable
4. Coding of Individual Case Safety Reports (ICSRs), if applicable
5. Communication of safety concerns to patients/consumers, healthcare professionals and regulatory authorities
6. Complaint handling
7. Deviation Documentation
8. Escalation of safety issues
9. Handling of Counterfeits
10. Internal audits
11. Literature searches (scientific and lay media)
12. Management of pharmacovigilance inspections
13. Manual handling of ICSRs, if applicable
14. ICSR collection, collation, follow up, assessment and reporting
15. Review and submission of regulatory documents (e.g. PSURs/PBRERs, RMPs)
16. Signal generation
17. SOP for SOPs
18. Training
19. Implementation of safety variations to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL), if applicable
20. Risk management system(s) and monitoring of the outcome of risk minimisation measures

Section VII: Pharmacovigilance system performance

Evidence of ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance should be described. The description of monitoring methods should include but not limited to the following.

1. An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 7-day and 28-day reporting over the past year;
2. A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by competent authorities regarding the quality of ICSR reporting, PSURs or other submissions;
3. Where applicable, an overview of the methods used to ensure timeliness of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
4. Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and explained and a list of performance indicators must be provided.

Section VIII: Pharmacovigilance Quality system

The pharmacovigilance quality system should include the following:

General Overview

A general description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance.

Document and Record Control

There should be a description of the archiving arrangements for electronic and/or hardcopy versions of the pharmacovigilance system master file, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents.

Procedural documents

The description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc) should be provided. The applicability of the various documents at global, regional or national level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance should be described.

A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided.

Training

Qualification and records of training for members of staff in the pharmacovigilance Departments of the Local Representative or the MAH and any individual that may receive safety reports, including employees of Local Distributors. Updated training materials and records of training programmes should be provided including assessment of the effectiveness of the training programmes as an Annex in the PSMF.

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the pharmacovigilance system master file.

A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex to the PSMF. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of third parties including Local Distributors. Where there are findings during the

audit, the corrective and preventive action plans for addressing these should be included in the Annex.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved.

Section IX: Annex to the PSMF

An annex to the pharmacovigilance system master file shall contain but not limited to the following documents:

1. A list of products covered by the pharmacovigilance system master file including the name of the product, the name of the active substance(s).
2. list of written policies and procedures for the purpose of complying with the FDA's pharmacovigilance requirements
3. A list of tasks that have been delegated by the qualified person for pharmacovigilance
4. A list of all completed audits, for a period of five years, and a list of audit schedules
5. Where applicable, a list of performance indicators
6. Updated training materials and records of the training should be provided including assessment of the effectiveness of the training programmes
7. Pharmacovigilance agreement between the MAH/Local Representative and the Local Distributor(s)