GOOD PHARMACOVIGILANCE PRACTICES (GVP) GUIDELINE
for
Marketing Authorization Holders (MAHs) in Bangladesh
(2023)

Directorate General of Drug Administration
Mohakhali, Dhaka-1212.

Health Services Division
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

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Health Services Division
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DISCLAIMER

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স্বাস্থ্য সেবা বিভাগ
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তারিখ: ১৩ ভাদ্র ১৪৩০
২৮ আগস্ট ২০২৩

প্রজ্ঞাপন

ঔষধ, ভ্যাকসিন ও মেডিকেল ডিভাইস ব্যবহারে পার্শ্ব/বিরূপ প্রতিক্রিয়া মনিটরিং এবং ফার্মাকোভিজিল্যান্স কার্যক্রম সুষ্ঠুভাবে পরিচালনার জন্য "Good Pharmacovigilance Practices (GVP) Guideline for Marketing Authorization Holders (MAH) in Bangladesh" এর প্রথম সংস্করণ অনুমোদিত হয়েছে।

০২। যথাযথ কর্তৃপক্ষের অনুমোদনক্রমে গাইডলাইনটি এতদসঙ্গে প্রেরণ করা হলো।

সংযুক্তি: অনুমোদিত গাইডলাইন।

রাষ্ট্রপতির আদেশক্রমে,

২৮-৮-২০২৩

মোহাম্মদ মোস্তাফিজুর রহমান
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তারিখ: ১৩ ভাদ্র ১৪৩০
২৮ আগস্ট ২০২৩

বিতরণ: সদয় জ্ঞাতার্থে ও কার্যার্থে (জ্যেষ্ঠতার ক্রমানুসারে নয়):

১) মন্ত্রিপরিষদ সচিব, মন্ত্রিপরিষদ বিভাগ, বাংলাদেশ সচিবালয়, ঢাকা।
২) মহাপরিচালক, স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা।
৩) মহাপরিচালক, ঔষধ প্রশাসন অধিদপ্তর, মহাখালী, ঢাকা (গাইডলাইনের নির্দেশনা প্রতিপালনের বিষয়টি সংশ্লিষ্ট সকলকে অবহিত করার অনুরোধসহ)।
৪) উপপরিচালক, বাংলাদেশ ফরম ও প্রকাশনা অফিস, তেজগাঁও, ঢাকা-১২০৮ (বাংলাদেশ গেজেটের পরবর্তী সংখ্যায় গাইডলাইনটি প্রকাশের অনুরোধসহ)।
৫) মন্ত্রীর একান্ত সচিব, স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়, ঢাকা (মাননীয় মন্ত্রীর সদয় অবগতির জন্য)।
৬) সচিবের একান্ত সচিব, স্বাস্থ্য সেবা বিভাগ, ঢাকা (সচিব মহোদয়ের সদয় অবগতির জন্য)।
৭) সিস্টেম এনালিষ্ট, স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়, ঢাকা (ওয়েব সাইটে প্রকাশের জন্য অনুরোধসহ)।
৮) জনাব .....।
৯) অফিস নথি।

Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

MESSAGE FROM THE HONORABLE MINISTER

I am pleased to know that Directorate General of Drug Administration has developed Good Pharmacovigilance Practices (GVP) guideline for ensuring the safety, efficacy, and quality of medicines and vaccines in Bangladesh. This guideline was developed following international best practices and Bangladesh country perspectives, in response to a recommendation of WHO assessors. The guideline is primarily needed for the marketing authorization holders, distributors, and importers of medicines and vaccines.

The GVP guideline provides an overview of adverse event reporting and management, periodic safety update reports, legal provisions of pharmacovigilance, setting up a pharmacovigilance wing in the industry, investigating serious adverse events, causality assessments, signal detection, risk management plans, and making regulatory decisions. It also defines the functions of users of the guideline as well as evaluators of adverse events. The guideline includes a comprehensive flow chart of the pharmacovigilance system in the country, an adverse event reporting form, and other relevant information.

I would like to convey my gratitude to the experts who contributed to develop the guideline and believes that it will help to promote knowledge about pharmacovigilance systems and their importance in ensuring medicine and vaccine safety.

I wish the best success of this initiatives and best wishes for all concerns bodies related to this issue.

Joy Bangla. Long live Bangladesh.

Zahid Maleque, MP
Minister
Ministry of Health and Family Welfare (MOHFW)
Government of The People's Republic of Bangladesh

Secretary
Health Services Division
Ministry of Health & Family Welfare
Government of the People's
Republic of Bangladesh

মুজিব বর্ষে স্বাস্থ্য খাত
এগিয়ে যাবে অনেক ধাপ

MESSAGE FROM THE HONORABLE SECRETARY

Good Pharmacovigilance Practices (GVP) guideline provides an overview of adverse events reporting and its management for ensuring safety of medicines and vaccines other than COVID- 19 and EPI program vaccines. Directorate General of Drug Administration (DGDA) is responsible for ensuring safety, efficacy, and quality of medicines and vaccines.

This protocol was developed following the international best pharmacovigilance practices as well as Bangladesh country perspectives in response to a recommendation of WHO assessors during the formal WHO global benchmarking of DGDA in 2021. It is mainly for the marketing authorization holders, distributors and importers of medicines and vaccines to follow.

The guideline provides an overview of reporting system which describes "what to report how to report adverse event, periodic safety update reports (PSUR), legal provision of pharmacovigilance that the DGDA and the industry should comply, setting up pharmacovigilance wing in industry how to investigate the serious adverse events (SAEs), causality assessments, signal detection, risk management plan, and making regulatory decision. It has defined the function of the users of this guideline as well as evaluators of adverse events.

This guideline also provides a comprehensive flow chart of pharmacovigilance system of the country, adverse event reporting form and relevant others.

I would like to convey my sincere thanks and gratitude to the experts who were actively involved in developing this guideline. I do believe, this guideline will help to gather knowledge about pharmacovigilance system, its importance and will contribute for ensuring medicine and vaccine safety.

Dr. Md. Anwar Hossain Howlader

Directorate General of Drug Administration
Ministry of Health and Family Welfare

MESSAGE FROM THE HONORABLE DIRECTOR GENERAL

I am very happy that DGDA has developed and finalized the Good Pharmacovigilance Practices (GVP) Guideline for Marketing Authorization Holders (MAH).

Directorate General of Drug Administration (DGDA) is responsible for ensuring quality, safety and efficacy of medicines, vaccines, medical devices etc. It has major functions like marketing authorization & registration, regulatory inspection, pharmacovigilance (PV), market surveillance & control, clinical trial oversight, licensing of premises, lab access, and lot release of vaccines. DGDA is the National Pharmacovigilance Centre (NPC) of Bangladesh and is the 120th member country of WHO-Uppsala Monitoring Centre (UMC), Sweden, the global platform for Pharmacovigilance. DGDA has access to UMC "VigiFlow", Vigibase & other tools for data entry and analysis.

In-depth information related to pharmacovigilance is required for defining the role of Marketing Authorization Holders (MAH) for creating culture of adverse events reporting. A formal WHO Global Benchmarking Tool (GBT) assessment took place at DGDA in July 2021, and one of the recommendations was to develop a new guideline specific for the pharmaceutical industry.

For this purpose, to ensure the safety, quality & efficacy of medicines and vaccines (other than COVID) DGDA formed a 17-membered working committee having experts from different disciplines and pharmaceutical industry under the leadership of Professor Md. Sayedur Rahman, Chairman, Pharmacology department of BSMMU as Chairperson. The committee sat together several times with the technical assistance of the US Agency for International Development (USAID)'s Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program and developed this guideline and shared it with the adverse drug reaction advisory committee (ADRAC) on March 21, 2022, for public consultation decision, and then with stakeholders including Bangladesh Association of Pharmaceutical Industries (BAPI) for their opinion and suggestion as a part of public consultation.

I express my sincere thanks and gratitude to the working committee of this guideline. I also express my gratitude to the Bangladesh Association of Pharmaceutical Industries (BAPI) and representatives from academia, pharmaceutical companies, Expanded Programme on Immunization (EPI), Directorate General of Health Services (DGHS), USAID MTaPS Program, WHO and DGDA whose support enriched the guideline. My thanks and gratitude to USAID MTaPS Program for its assistance throughout the development process of the guideline.

In this guideline there are eight modules for the pharmaceutical industry and DGDA to follow. These are: General Information on Pharmacovigilance, Pharmacovigilance Quality Management System, Individual Case Safety Report (ICSR) Management, Risk Management Plan, Preparation & Submission of PSURS, Pharmacovigilance System Maser File (PSMF), Pharmacovigilance Inspections and Miscellaneous. I expect that this guideline will help all concerned to facilitate the establishment of pharmacovigilance set up at industry level, regular practice of pharmacovigilance, understanding and complying with legal provision, adverse event reporting, risk management, safety updates of individual product etc. for ensuring patient safety.

Major General Mohammad Yousuf
Director General
Directorate General of Drug Administration
04 DEC 2022

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We express our gratitude to Major General Mohammad Yousuf, Director General of the DGDA, for his exceptional leadership and unwavering guidance throughout the development of this guideline. Furthermore, we extend our appreciation to Major General (Rtd.) Md Mahbubur Rahman, former Director General of DGDA, for taking the initiative to develop this guideline and for his instrumental role in forming the working committee. Our sincere thanks are also extended to the diligent members of the working committee responsible for preparing this guideline, including the Technical Sub-Committee (TSC) and the Adverse Drug Reaction Advisory Committee (ADRAC). Their invaluable contributions have significantly enriched the content of this guideline. We would like to acknowledge and express our appreciation to all DGDA officials and stakeholders, Development Partners including the US Agency for International Development (USAID)'s Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program who provided their unwavering guidance and support at every stage of the guideline development process. The guideline was developed and published with the technical assistance of USAID MTaPS Program.

We extend sincere gratitude to the following experts for dedicating their time and providing their technical input in the development of this guideline:

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3. **Professor Md. Sayedur Rahman,** *Chairman, Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University, Dhaka*
4. **Professor Sitesh Chandra Bachar,** *Dean, Faculty of Pharmacy, Dhaka University*
5. **Professor Dr Md Abdur Rahman,** *Faculty of Pharmacy, Dhaka University*
6. **Professor Dr. Zakir Hossain Galib,** *Dermatology Department, Sir Salimullah Medical College, Mitford, Dhaka.*
7. **Dr. Md. Akter Hossain,** *Director (cc) and Head of Pharmacovigilance Department, DGDA*
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9. **Dr. S.M. Shahida,** *Associate Professor, Gynae Department, Dhaka Medical College, Dhaka*
10. **Colonel Md. Shahjahan Siraj,** *Dermatologist, Department of Skin & VD, CMH, Dhaka*
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15. **Mr. Md. Shamim Alam Khan,** *Director and Head of PV, UniMed & UniHealth Pharmaceuticals Ltd*
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18. **Dr. Md Rasel Raihan,** *Country Patient Safety Head, Novartis (Bangladesh) Limited*
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20. **Dr. Sadia Afrin,** *Drug Safety Physician, Pharmacovigilance (Medical Affairs), Beximco Pharmaceuticals Limited*
21. **Dr. Selina Ahmed,** *Former National Professional Officer, WHO, Bangladesh*
22. **Ms. Gulshan Jahan,** *Assistant Director and former Member-Secretary, ADRM Cell, DGDA*
23. **Mr. Mahbub Hossain,** *Assistant Director and Member-Secretary, ADRM Cell, DGDA*
24. **Mr. Md. Abul Kalam Azad,** *Senior Technical Advisor, USAID MTaPS Program*
25. **Mr. Md. Moshiur Rahman,** *Superintendent of Drugs and Member of ADRM cell, DGDA*
26. **Mr. Rajib Das,** *Inspector of Drugs and Member of ADRM cell, DGDA*

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I. MODULE ONE: GENERAL INFORMATION ON PHARMACOVIGILANCE

Before a product is marketed, experience of its safety and efficacy are limited to its use in clinical trials. The conditions under which patients are studied pre-marketing do not necessarily reflect the way the product will be used in hospitals or in general practice once it is marketed.

No matter how extensive the pre-clinical work in animals and the clinical trials in patients, certain adverse effects may not be detected until a very large number of people have used the medicinal product or medical devices.

The Adverse Drug Reaction Monitoring (ADRM) cell, DGDA is responsible for product safety monitoring including Adverse Event/Adverse Event Following Immunization (AEFI) Reporting.

A. Objectives of Pharmacovigilance

- To identify previously unrecognized adverse events or changes in the patterns of adverse effects
- To prevent harm from adverse events arising from the use of medicinal products or medical devices.
- To assess the risks and benefits of products in order to determine what actions, if any, are necessary to improve their safe use
- To promote the safe and effective use of medicinal products, particularly through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public as well as to monitor the impact of any action taken.

B. Scope of Pharmacovigilance

The scope of pharmacovigilance in Bangladesh includes (but is not limited to):

- AE/AEFI reporting by healthcare professionals, consumers and MAH, collection of reports and monitoring by MAH and the Authority.
- Safety profile monitoring, as well as preparation and evaluation of Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP).
- Risk Management System: a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.
- Safety communication (for example: Direct Healthcare Professional Communication (DHPC) Letter, Package insert (PI), websites and publications to ensure product information (label, package insert) are updated with latest safety information according to DGDA directives and circulars.

C. Legal Basis

The legal basis of this guideline can be found in National Drug policy 2016, section 4.13 (addendum 23 March 2017) and the Bangladesh Gazette 2021 on Pharmacovigilance in the country.

D. Confidentiality

The Authority will maintain strict confidentiality with regards to the identity of patients and reporters.

II. MODULE TWO: PHARMACOVIGILANCE QUALITY MANAGEMENT SYSTEM

This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorization holders for performing their PV activities.

A pharmacovigilance system is defined as a system used by an organization to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of DGDA registered products (medicinal products, vaccines-biologics and medical devices) and detect any change to their risk-benefit balance.

A pharmacovigilance system, like any system, is characterized by its structures, processes and outcomes. For each specific pharmacovigilance process, including its necessary structures, a dedicated Module is included in GVP.

A. The Basic PV System

PV system should consist of at least all of the following:

I. Collection and management of data on product safety, including individual AE/AEFI reporting

II. Data evaluation and any decision-making with regards to safety issues

III. Pro-active risk management activities to minimize any potential risk associated with the use of a product

IV. Action and communication with stakeholder(s) to protect public health (including but not limited to):

- Product information (label, package insert) should be kept up-to-date to ensure that there is no undue delay in updating documents.
- Fulfill registration requirement/condition and carry out any risk minimization measure (e.g. special registration condition, RMP and regulatory action due to emerging safety issues).

V. Pharmacovigilance audit: Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities. The audit strategy should cover all parts of the pharmacovigilance system including:

- All pharmacovigilance processes and tasks
- The quality system for pharmacovigilance activities
- Interactions and interfaces with other departments, as appropriate
- Pharmacovigilance activities conducted by affiliated organizations or activities delegated to another organization (e.g. MAH or third parties, such as contract organizations and other vendors)
- Preparation of audit reports and follow-up audits, including their dates and results.

VI. Training of the pharmacovigilance personnel: Quality and Adequacy of training, qualifications and experience of staff.

B. Qualified Person for Pharmacovigilance (QPPV)

I. A description of the responsibilities guaranteeing that the QPPV has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance.

II. A summary curriculum vitae with the key information on the role of the QPPV responsible for pharmacovigilance, contact details; details of backup arrangements to apply in the absence of the qualified person responsible for pharmacovigilance.

III. The QPPV should be based in Bangladesh. QPPV must be contactable by the Authority at all times. QPPV must have experience or training in PV so that he or she understands his or her roles as QPPV. If the QPPV is not a healthcare professional, he or she should have access to a medically qualified person.

IV. The MAH should ensure there are back-up personnel for QPPV who are contactable whenever needed in the absence of the QPPV. The QPPV should ensure that the back-up person has all the necessary information to fulfil the role.

V. The MAH must provide the Authority with the details of the QPPV and Deputy QPPV (including full name, company's position, postal address, email address, telephone, hand phone number and fax numbers). Any changes of these details should promptly be informed to the Authority.

VI. The roles of the QPPV are as follows (but not limited to):

- To establish an effective system for monitoring AE/AEFIs associated with the use of products registered under the MAH
- To ensure that information pertaining to AE/AEFIs which come to the knowledge of the MAH, including through medical representatives, is collected and collated so that it is accessible at a single point
- To ensure that all local AE/AEFI reports are submitted to the Authority in a timely manner
- To ensure all relevant safety information such as PSUR, post-registration study reports and RMP are submitted
- To ensure all risk minimization plan (e.g. DHPC, patient guide etc.) have been carried out
- To ensure that any request for additional benefit-risk information by the Authority is answered fully and promptly;
- To alert the Authority of any emerging safety issue(s) involving products registered under the MAH;
- The QPPV may delegate specific tasks, under supervision, to appropriately qualified or trained individuals, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.
- Maintain up to date PV Organization Structure

C. Engagement of a Third Party on PV Activities

I. There are situations where the MAH may engage a third party on certain PV activities of the PV system (e.g., ICSR processing, submission, PSUR management, literature screening etc.). These third parties may need to be enlisted by DGDA. The MAH shall nevertheless retain full responsibility for ensuring the quality, efficacy, and integrity of the PV system.

II. This guideline also applies to the other organization or third party to which the tasks have been contracted.

III. When engaging a third party, the MAH shall draw up detailed and up-to-date contractual agreements or letters of appointment, or official documents. These should clearly document the contractual arrangements between the MAH and the other organization, describing arrangements for delegation and the responsibilities of each party.

IV. In such relationships, it is very important that the contractual agreements or letter of appointment or official document specify the processes for the exchange of safety information, including timelines and regulatory reporting responsibilities. Processes should be in place to avoid duplicate reporting to the Authority.

V. When the transfer of pharmacovigilance data occurs between organizations that have set up contractual agreements or letters of appointment or official documents, there should be a confirmation and/or reconciliation process to ensure that all notifications are exchanged.

D. Training of Personnel for Pharmacovigilance

I. Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organization is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel.

II. All personnel involved in the pharmacovigilance activities shall receive initial and continued training. For MAH, this training shall relate to the roles and responsibilities of the personnel.

III. The organization shall keep training plans and records for documenting, maintaining and developing the competencies of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.

IV. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organization should receive and be able to seek information about what to do if they become aware of a safety concern.

V. Adequate training should also be considered by the organization for staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to activities related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs, legal affairs.

VI. Appropriate instructions on the processes to be used in case of urgency, including business continuity, shall be provided by the organization to their personnel involve in pharmacovigilance activities.

E. Safety Record Management

I. All pharmacovigilance data and documents relating to individual registered medicinal products must be retained for as long as the product registration exists and for at least an additional 5 years after the product registration has ceased to exist.

II. The documents and records must be archived during the retention period. However, the documents and records must be retrievable whenever requested by the Authority.

III. MODULE THREE: INDIVIDUAL CASE SAFETY REPORT (ICSR) MANAGEMENT

This Module highlights the requirements for data collection, recording and submission of individual reports of adverse events associated with medicinal products registered for human use in Bangladesh.

A. Source of ICSRs

Marketing authorization holders should take appropriate measures to collect and collate all reports of adverse events associated with medicinal products originating from unsolicited or solicited sources.

1. Unsolicited ICSRs

I. Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a competent authority, marketing authorization holder that describes one or more suspected adverse events in a patient who was given one or more medicinal products. It does not derive from a study or any organized data collection systems.

II. Medical Information Query

The MAH should screen any unsolicited enquiries of a medical, scientific, or clinical nature pertaining to a product, disease state or therapeutic area for potential reports of suspected AE.

- Unsolicited cases of suspected AE from medical inquiries should be handled as spontaneous reports.

III. Suspected adverse AE related to Quality Complaints

The MAH should screen all Product quality Complaints expressed in the form of explicit or implicit technical or quality defects which may or may not be accompanied with adverse events and/or special case scenarios for potential report of AE.

- Unsolicited cases of AE from quality complaints should be handled as spontaneous reports.
- Solicited cases of AE from quality complaints should be handled as study reports.
- The Investigation summary report of Product quality complaints with AE should also be submitted following the reporting period based on report type.

IV. Literature Reports

Scientific and medical literatures are a significant source of information for the monitoring of safety profile and benefit-risk balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues.

V. Information on Suspected AE from Internet or Digital Media

- MAH should regularly screen their own/sponsored website and digital media for potential reports of AE. The frequency of the screening should allow potential valid AE to be reported to the Authority within the stipulated timelines
- Unsolicited cases of AE from the internet or digital media should be handled as spontaneous reports.
- When collecting reports of suspected AE via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient of the existence of a real person based on the information available e.g. an email address under a valid format has been provided.

VI. Reports from non-medical sources

If a marketing authorization holder becomes aware of a report of suspected adverse events originating from a non-medical source, for example the lay press or other media, it should be managed as a spontaneous report. Every attempt should be documented to follow-up the case to obtain the minimum information that constitutes a valid ICSR.

VII. Report from Health Authority (HA)

DGDA may receive suspected adverse events from sources other than MAHs like Health Care Professionals (HCPs), directly from patient, Public Health Programs (PHPs), Health Facilities (HF), Non-Government Organizations (NGOs), other regulatory authorities, etc. DGDA will assess initial information and if required may forward the case to MAHs for further information or follow up.

If a marketing authorization holder becomes aware of a report of suspected adverse events originating from local HA, it should be managed as a spontaneous report. Every attempt should be documented to follow-up the case to record the minimum information that constitutes a valid ICSR.

VIII. Contractual/Business partners

There are situations where the MAH may engage with contractual/business partners for certain activities like toll manufacturing, co-promotion, sales and distribution activity, etc. Any AE received by the contractual/business partners should be forwarded to MAH as per agreement between MAH and contractual/business partners. The MAH shall nevertheless retain full responsibility in ensuring the quality, efficacy, and integrity of the PV system.

In such relationships, it is very important that the contractual agreements or letter of appointment or official document specify the processes for exchange of safety information, reconciliation including timelines and regulatory reporting responsibilities.

IX. Compassionate Use/Named Patient Use/Pre Approval Access

Where an organization (e.g. sponsor, applicant, MAH, hospital or wholesaler) or a healthcare professional is supplying a medicinal product under ‘compassionate use’ or ‘named patient use’ or Pre-approval Access e.g., Managed Access Program (MAP), it should be strictly controlled and be subjected to protocol.

The protocol should clearly describe the responsibility on the reporting of the AE suspected of being related to use of the medicinal product. The organization supplying the medicinal product should continuously monitor the balance of benefit and risk of drugs used under such conditions.

AE from such program should be handled as spontaneous reports.

2. Solicited Reports

Solicited reports are defined by the ICH as those derived from organized data collection systems, which include clinical trials, registries, information gathering on efficacy.

For the purposes of safety reporting, solicited reports should be classified as study reports

I. Post Marketing Surveillance Study

Studies subjected to post-market AE reporting requirements (e.g. phase IV studies) should be monitored in a way that ensures that all AE especially, serious/ non serious, expected/ unexpected, including unusual failure in efficacy for new drugs, are reported to the MAH by the investigator(s) so that the MAH can provide such reports to the Authority.

MAH should help investigators understand their role in assessing the possible relationship between an adverse event and the administration of a product during post-marketing studies.

Comparator and concomitant products used in these studies are within the scope of this guideline. It is the sponsor's responsibility to decide whether or not the active comparator and concomitant product cause the AEs and whether or not it should be reported to the other MAH and/or directly to the Authority.

B. Validation of ICSRs

Only valid ICSR qualifies for HA submission. All reports of suspected adverse events should be validated before submitting to health authority to make sure that the minimum criteria are included in the reports.

1. Identifiable Reporter (Primary Source)

The term 'identifiable' indicates that the organization notified about the report has enough evidence of the existence of the person who reports the facts based on the available information characterized by qualification (e.g. physician, pharmacist, other healthcare professional, consumer or other non-healthcare professional) name, initials or address. Whenever possible, contact details of the reporter should be recorded so that follow-up activities can be performed.

However, if the reporter does not wish to provide contact details, the AE report(s) should still be considered as valid, providing that the organization who was informed of the case is able to confirm it directly with the reporter.

All parties providing case information or are approached for case information should be identifiable and recorded, not only the initial reporter. If information on the reporter's qualification is missing, the notification should be considered by default as a consumer report.

2. Identifiable Patient

The term 'identifiable' refers to the possibility of verification of the existence of a patient based on the available information. Qualifying descriptor characterized by initials, patient identification number, date of birth, age, age group and/or gender. The information should be as complete as possible.

An AE report should not be considered valid for submission unless information is available for at least one of the patient qualifying descriptors as explained above.

Furthermore, in the absence of a qualifying descriptor, a notification referring to a definite number of patients should not be regarded valid until an individual patient can be characterized by one of the qualifying descriptors for creating a valid AE report.

3. Suspected Substance/Medicinal Product

A drug to be used as an ingredient of a preparation for a medicinal purpose. Interacting substances or medicinal products should also be considered suspected.

4. Suspected Adverse Event

A valid report should contain at least one specific AE. The report does not qualify as a valid AE report if it is reported that the patient experienced an unspecified adverse event and there is no information on the type of adverse event.

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR. MAHs are expected to exercise due diligence in following-up the case to collect the missing data elements and follow-up activities should be documented. Reports, for which the minimum information is incomplete, should be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.

C. Follow-up of ICSR

When first received, the information in adverse events reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.

MAH should submit follow-up AE reports if significant new medical information has been received. Significant new information relates to, for example, a new adverse event, a change in the causality assessment, and any new or updated information on a case that impacts on its medical interpretation. Medical judgement should therefore be applied for the identification of significant new information requiring to be submitted as follow-up AE report.

D. Reporting requirements in Special situations

1. Use of a Medicinal Product during Pregnancy or Breastfeeding

MAH must establish surveillance systems of pregnant or breastfeeding patients for the purpose of collating experience on the usage and outcome of products used in these groups. MAH must report AE related to pregnancy and breastfeeding regardless of whether or not the product is contraindicated in this situation.

I. Pregnancy

Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product.

Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports, which have a normal outcome, should not be reported since there is no AE. These reports should however be collected and discussed in the periodic safety update reports.

II. Breastfeeding

AE/AEFI(s), which occur in infants following exposure to a medicinal product from breast milk, should be reported in accordance with the criteria outlined in this guideline.

2. Use of a Medicinal Product in Pediatric or Elderly Population

The collection of safety information in the pediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a healthcare professional or consumer reports a case. This will enable the identification of potential safety signals specific to a particular population.

3. Lack of Efficacy

Reports of lack of efficacy should also be submitted to the Authority. Clinical judgement should be used in reporting. This applies unless the reporter has specifically stated that the outcome was due to disease progression and not related to the medicinal product.

4. Reports of Overdose, Abuse, Off-Label Use, Misuse, Medication Error or Occupational Exposure

Reports of overdose (either accidental or intentional), abuse, off-label use, misuse, medication error or occupational exposure, which has led to an AE, should be reported to the Authority.

Reports with no associated AE should not be reported as individual case reports. They should be considered in PSUR as applicable. When those reports constitute safety issues affecting the benefit-risk balance of the medicinal product, they should be notified to the Authority.

These reports should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, and context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unregistered indication or population, etc.).

E. Submission of individual case safety reports (ICSRs)

1. Submission time frames of ICSRs

Only valid locally reported ICSRs should be submitted. The clock for the submission of a valid ICSR starts as soon as the information containing the minimum criteria has been brought to the attention of any personnel of the marketing authorization holder, including medical representatives and contractors. This date should be considered as day zero. It is the first day when a notified marketing authorization holder gets knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. The timelines for submission of unsolicited and solicited reports under this guideline are based on calendar days.

- Inform the DGDA (ADRM Cell) of any serious AE arising from the use of its registered products immediately and no later than 15 calendar days after the reporting of such adverse events
- Inform the DGDA (ADRM Cell) of any non-serious AE arising from the use of its registered products no later than 30 calendar days after the reporting of such adverse events
- This applies to initial and follow-up information
- Where an ICSR is initially submitted as serious becomes non-serious based on new follow-up information, this follow up information should still be submitted within 15 days; the submission time frame for non-serious reports should then be applied for the subsequent follow-up reports
- Where an ICSR is initially submitted as non-serious becomes serious based on new follow-up information, this information should be submitted within 15 days; the submission time frame for serious reports should then be applied for the subsequent follow-up reports

2. Modalities for submission of individual case safety reports (ICSRs)

AE reports can be submitted to the Authority via the following routes:

- Online reporting: via DGDA website/Apps
- Post to DGDA or Hard Copy via DGDA office (as per Annex I or Any mutual template e.g., CIOMS)
- Email or Fax (as per Annex I or Any mutual template e.g., CIOMS)
- Electronic Submission (using E2B/CIOMS/Any mutual template)

IV. MODULE FOUR: RISK MANAGEMENT PLAN

A. Introduction

A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Generally, a medicinal product will be associated with adverse events and these will vary in terms of severity, the likelihood of occurrence, effect on individual patients and public health impact. However, not all adverse events and risks will have been identified at the time when an initial marketing authorization is granted and some will only be discovered and characterized in the post-authorization phase. The aim of a risk management plan (RMP) is to document the risk management system considered necessary to identify, characterize and minimize a medicinal product's important risks. To this end, the RMP contains:

- The identification or characterization of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');
- The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse events (the 'pharmacovigilance plan');
- The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the 'risk minimization plan').

B. Terminology

RMP should focus on those risks that are relevant for the risk management activities for the authorized medicinal product.

From the **identified risks** of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is sufficient scientific evidence that they are caused by the medicinal product. Reports of adverse reactions may be derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature. They may be linked to situations such as off label use, medication errors or drug interactions. Not all reported adverse reactions are necessarily considered a relevant risk of the product in a given therapeutic context.

From the **potential risks** of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.

The RMP should focus on **the important identified risks** that are likely to have an impact on the risk benefit balance of the product. An important identified risk to be included in the RMP would usually warrant:

- Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk);
- Risk minimization activities: product information advising on specific clinical actions to be taken to minimize the risk, or additional risk minimization activities.

The **important potential risks** to be included in the RMP are those important potential risks that, when further characterized and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Where there is a scientific rationale that an adverse clinical outcome might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product, the adverse reaction should be considered a potential risk, and if deemed important, should be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

Missing information relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilization (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

C. Responsibilities of MAH for Risk Management

An applicant/marketing authorization holder is responsible for:

- having an appropriate risk management system in place
- Ensuring that the knowledge and understanding on the product's safety profile, following its use in clinical practice, are critically reviewed. The marketing authorization holder should monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products and update the risk management system and the RMP accordingly, as described below.
- The critical review of the safety profile of the product is a continuous activity and is reflected in data submitted with periodic safety update reports (PSUR), where an RMP submission may or may not be warranted.

D. Structure of the Risk Management Plan

1. Product(s) Overview
2. Safety Specification
    - Module SI Epidemiology of the indication(s) and target population(s)
    - Module SII Non-clinical part of the safety specification
    - Module SIII Clinical trial exposure
    - Module SIV Populations not studied in clinical trials
    - Module SV Post-authorization experience
    - Module SVI Additional EU requirements for the safety specification
    - Module SVII Identified and potential risks
    - Module SVIII Summary of the safety concerns
3. Pharmacovigilance plan (including post-authorization safety studies)
4. Plans for post-authorization efficacy studies
5. Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
6. Summary of the risk management plan

1. Product(s) Overview

This should provide the administrative information on the RMP and an overview of the product(s). The information presented should be current and accurate in relation to the ongoing application as it is anticipated to appear in the marketing authorization. The information should include:

Active substance information:

- active substance(s);
- pharmacotherapeutic group(s) (ATC code);
- name of the MAH or applicant
- Medicinal product(s) to which this RMP refers.
- brief description of the product including:
  - chemical class;
  - summary of mode of action;
  - important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- indications: approved and proposed (if RMP submitted with an extension/restriction of indication);
- dosage
- pharmaceutical forms and strengths;
- whether the product is subject to additional monitoring in the EU (at initial marketing authorisation application conclusion or with RMP updates).

2. Safety Specification

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s).

It should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used e.g. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine the understanding of the benefit-risk profile during the post-registration period.

In the RMP, the safety specification will form the basis of the pharmacovigilance plan, and the risk minimization plan.

I. Module SI: Epidemiology of the indication(s) and target population(s)

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, but the emphasis should be on the epidemiology in the country of the proposed indication.

II. Module SII: Non-clinical part of the safety specification

This RMP module should present a summary of the important non- clinical safety findings, for example:

a) Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);

b) General pharmacology (e.g. Cardiovascular, including QT interval prolongation, nervous system);

c) Drug interactions;

d) Other toxicity-related information or data.

III. Module SIII: Clinical trial exposure

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables or graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomized blinded trial population only and all clinical trial populations). Stratifications would normally include:

- Age and gender;
- Indication;
- Dose;
- Racial origin.

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format.

The exposure of special populations (pregnant women, breastfeeding women, renal impairment, hepatic impairment, cardiac impairment, subpopulations with relevant genetic polymorphisms, immune-compromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism.

The categories above are only suggestions and the use of tables or graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied, and route of administration, number of courses/immunizations or repeat administrations may be important categories to be added.

IV. Module SIV: Populations not studied in clinical trials

Populations that are considered under missing information should be described in this RMP module.

Information on the low exposure of special populations or the lack thereof (e.g. pregnant women, breast-feeding women, patients with renal impairment, hepatic impairment or cardiac impairment, populations with relevant genetic polymorphisms, immuno-compromised patients and populations of different ethnic origins) should be provided where available and as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the type of genetic polymorphism, as available.

If the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP. Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. "on-label", and if the use in such populations might be associated with risks of clinical significance. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria. When such populations are proposed as missing information, then RMP module SIV should also include a discussion on the relevant subpopulations.

If there is evidence that use in excluded populations is associated with an undesirable clinical outcome, then the outcome should be included as an important (potential) risk.

V. Module SV: Post-authorization experience

This module should include discussion on post-marketing data that are available from post-authorization experience in other regions where the product is already registered or post-marketing data from other registered products containing the same active substance from the same MAH. It should only provide an overview of experience in the post-authorization phase to help in risk management planning purposes.

Additionally, a discussion on how the product is being used in practice and on-label and off-label use, including its use in the special populations mentioned in RMP module SIV, may also be included when relevant for the risk identification discussion in module SVI.

VI. Module SVI: Additional requirements for the safety specification

In addition to safety topics, the following should be addressed in the RMP: the potential for misuse for illegal purposes, and, where appropriate, the proposed risk minimization measures, e.g. limited pack size, controlled access programme, special medical prescription.

VII. Module SVII: Identified and potential risks

This RMP module provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events. It may also include other safety topics that may lead to risks of the product such as potential harm from overdose, potential risks resulting from medication errors and off-label use, potential for transmission of infectious agents from the manufacturing process, the important pharmacological class effects, the important pharmacokinetics and pharmacodynamics interactions and the risks associated with the administration procedure and disposal of the used product.

VIII. Identification of Safety Concerns in the Initial RMP Submission

Initial identification of safety concerns (important identified and important potential risks during the initial application for registration or post-registration (e.g. for approved products that previously did not have an RMP). This section is expected to be "locked" and not change after approval of the initial RMP.

IX. Risks Considered Important for Inclusion in the List of Safety Concerns and Risks Not Considered Important for Inclusion in the List of Safety Concerns

The following information should be summarized and discussed in this section: risk seriousness, risk frequency and the benefit-risk impact of the risks.

For risks not taken forward as safety concerns, the information can be grouped by reasons for not including them as safety concerns.

- **New Safety Concerns and** Reclassification **with A Submission of An Updated RMP**

When an important identified or potential risk or missing information is re-classified or removed, a justification should be provided in this section, with appropriate reference to the safety data.

- **Details of Important Identified and Potential Risks and Missing Information**

For RMPs containing multiple products, if there are significant differences between products (e.g. fixed dose combination products) it is appropriate to make it clear which safety concerns relate to which product.

This RMP section applies to all stages of the product's life cycle.

Presentation of important identified risks and important potential risks data:

- name of the risk ;
- potential mechanism;
- evidence source(s) and strength of the evidence (i.e. the scientific basis for suspecting the association);
- characterization of the risk: e.g. frequency, absolute risk, relative risk, severity, reversibility, long- term outcomes, impact on quality of life;
- risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (i.e. predictability of a risk; whether risk factors have been identified that can be minimized by routine or additional risk minimization activities other than general awareness using the PI; possibility of detection at an early stage which could mitigate seriousness);
- impact on the risk-benefit balance of the product;
- public health impact (e.g. absolute risk in relation to the size of the target population and consequently actual number of individuals affected, or overall outcome at population level).

Presentation of missing information data:

- name of the missing information ;
- evidence that the safety profile is expected to be different than in the general target population
- description of a population in need of further characterization, or description of the risk anticipated in the population not studied, as appropriate.

X. Module SVIII: Summary of the safety concerns

A list of safety concerns should be provided with the following categories:

- important identified risks;
- important potential risks;
- missing information.

3. Pharmacovigilance plan (including post-authorization safety studies)

The purpose of the pharmacovigilance plan is to discuss how the applicant/marketing authorization holder plans to further characterize the safety concerns in the safety specification. It provides a structured plan for:

- the investigation of whether a potential risk is confirmed as an identified risk or refuted;
- further characterization of safety concerns including severity, frequency, and risk factors;
- how missing information will be sought;
- measuring the effectiveness of risk minimization measures.

The pharmacovigilance plan should focus on the safety concerns summarized in RMP module SVIII of the safety specifications and should be proportionate to the benefits and risks of the product. Early discussions between competent authorities and the applicant/marketing authorization holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed and consequently milestones should be agreed.

Pharmacovigilance activities can be divided into routine and additional pharmacovigilance activities.

This RMP section should describe only the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. The MAH should list in this RMP section their planned additional pharmacovigilance activities, detailing what information is expected to be collected that can lead to a more informed consideration of the benefit-risk balance.

Additional pharmacovigilance activities are pharmacovigilance activities that are not considered routine. The post-authorization safety studies (PASS) may include non-clinical studies, clinical trials or non-interventional studies. Examples include long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterization of the long-term safety of the product.

PASS aim to identify and characterize risks to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimization activities. They should relate to the safety concerns identified in the safety specification, be feasible and should not include any element of a promotional nature.

PASS should be designed and conducted according to the respective legislation in place. Study protocols may be included for evaluation in an RMP update only when the studies are included in the pharmacovigilance plan and the protocols submission has been requested by the competent Authority. Protocols of completed studies should be removed from RMP once the final study reports are submitted to the competent Authority for assessment and the study is removed from the pharmacovigilance plan. The milestone for the final study report submission to the competent Authority should be included for all studies in the pharmacovigilance plan.

4. Plans for post-authorization efficacy studies

This RMP part should include a list of post-authorization efficacy studies (PAES) imposed as conditions to the marketing authorization or when included as specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances. If no such studies are required, RMP Part IV may be left empty.

5. Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

The risk minimization plan should provide details of the risk minimization measures which will be taken to reduce the risks associated with individual safety concerns.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimization plan specific to each product, e.g. products where the indications lie in different medical specialties and have different safety concerns associated; products where risks differ according to target population; products with legal status for the supply of medicinal products to patients.

The need for continuing risk minimization measures should be reviewed at regular intervals and the effectiveness of risk minimization activities assessed.

Risk minimization activities may consist of routine risk minimization (e.g. measures associated with locally approved package insert) or additional risk minimization activities (e.g. DHPC/educational materials/ controlled distribution systems). All risk minimization measures should have a clearly identifiable objective.

a) Routine Risk Minimization Activities

Routine risk minimization activities are those which apply to every medicinal product. These relate to:

1) Package insert;

2) Product label(s);

3) Pack size(s);

4) Legal status of the product.

(1) Additional Risk Minimization Activities

Additional risk minimization activities, if proposed, need to be provided in detail with a justification for the proposed activity. The need to continue such measures should be periodically reviewed by the MAH. Any subsequent changes/updates should be notified and approved by DGDA prior to implementation.

(2) Summary of Risk Minimization Measures

A table summarizing the routine and additional risk minimization activities by safety concern should be provided.

6. Summary of the risk management plan

The summary must include key elements of the RMP with a specific focus on risk minimization activities. With regards to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.

The RMP summary should be updated when important changes are introduced into the full RMP. Changes should be considered important if they relate to the following:

I. New important identified or potential risks or important changes to or removal of a safety concern;

II. Inclusion or removal of additional risk minimization measures or routine risk minimization activities recommending specific clinical measures to address the risk;

III. Major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

7. Bangladesh -Specific Annex (BSA) for RMP

A Bangladesh -Specific Annex (BSA) or Global GVP standard RMP is required for RMP submission. If MAH doesn't have Global GVP standard RMP, then RMP needs to be submitted in BSA format only. The BSA should provide Bangladesh specific information and includes the following sections:

- Product overview in Bangladesh
- Changes from previous RMP version
- Summary of changes to the BSA over time
- Safety specification: summary of safety concerns in relation to the approved indication(s) in Bangladesh.
- Description of local pharmacovigilance plan
- Description of local risk minimization plan
- Additional Information (if applicable):
- Latest version of the proposed/approved package insert and product information in bangladesh.
- Details of local additional pharmacovigilance activities, e.g.:
- Tabulated summary of planned, ongoing and completed pharmacovigilance study programme;
- Protocols for proposed, ongoing, and completed studies in pharmacovigilance plan;
- Specific adverse event follow-up forms;
- Protocols for proposed and ongoing studies.

a) Details of local risk minimisation activities, e.g.:

i) Approved Direct Healthcare Professional Communication (DHPC) Letter;

ii) Educational materials provided to healthcare professionals (English version) and patients (both English and Bangla versions).

b) Other supporting data (including referenced materials)

i) Any additional risk minimization activities/programs requested by other regulatory authorities (e.g.: US FDA, EMA)should be provided.

The appended **Template for Bangladesh-Specific Annex (BSA) for RMP** should be followed as per Annex II.

E. Situations when a Risk Management Plan should be submitted

1. Submission of RMP during registration

I. A new medicine (molecule) that is introduced for the first time in Bangladesh. This molecule will be considered to be "new" for a period of four years from the date of first approval. Any MAH for this new medicine (molecule) should submit RMP.

II. During registration for biologics and vaccines irrespective of new or old molecule

RMP should be submitted using the Bangladesh Specific Format for RMP (Annex II) or global GVP standard RMP format.

2. Post-Registration Submission Requirement

In the post-registration phase, an update for the products under above mentioned categories along with the template of Bangladesh Specific Format (Annex II) or global GVP standard RMP format is expected to be submitted in the following situations:

I. When there is a significant change to the benefit-risk balance of one or more medicinal products included in the RMP;

II. When there is an application involving a significant change to an existing registered product, such as:

- New or significant change in indication;
- New dosage form;
- New route of administration;
- New manufacturing process of a biotechnologically-derived product;
- New chemical form;
- New dosage strength.

III. When there is a change in the list of the safety concerns or any changes in the existing additional pharmacovigilance or additional risk minimization activities;

IV. At the request of the Health Authority when there is a concern on a risk affecting the benefit-risk balance.

3. Submission of RMP for Products Other than New Drug Products/ Biologics

Generally, RMPs for all medicinal products are not required. However, a RMP may be requested by Health Authority when there is a safety concern affecting the benefit-risk balance of the registered product. It is expected that the MAH will monitor the safety of their products on the market.

V. MODULE FIVE: PREPARATION & SUBMISSION OF PSURs

A. Introduction

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.

The preparation of PSUR for regulatory authorities is a routine pharmacovigilance activity outlined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2E guidelines.

The marketing authorization holder shall prepare a single PSUR for its medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments.

B. Objectives of the periodic safety update report (PSUR)

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the risk benefit balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. The PSUR is therefore a tool for post authorization evaluation at defined time points in the lifecycle of a product.

C. Principles for the preparation of PSURs

MAH shall prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly. There might be exceptional scenarios where the preparation of separate PSURs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the relevant competent authorities preferably at the time of authorization. The format and table of contents of all PSURs shall be as described in the Annex III and each report should include interval as well as cumulative data.

D. General Information of PSUR:

The PSUR should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

I. Summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;

II. Summarising any important new efficacy or effectiveness information that has become available during the reporting interval;

III. Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile;

IV. Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When appropriate, the PSUR should include proposed action(s) to optimize the benefit-risk profile. Urgent safety information should be reported through the appropriate mechanism; the PSUR is not intended to provide initial notification of significant new safety information or to provide the means by which new safety concerns are detected.

E. Submission schedule of PSURs

Generally, PSUR for all medicinal products are not required.

The MAH shall submit PSURs for

I. A new medicine (molecule) that is introduced for the first time in Bangladesh. This molecule will be considered to be "new" for a period of four years from the date of first approval. Any MAH for this new medicine (Molecule) should submit PSUR.

II. All Biologics and vaccines irrespective of new or old.

PSUR should be submitted using the Bangladesh Specific Annex for PSUR (Annex III) and/or global GVP standard format.

The MAH shall submit PSURs according to the following submission schedule

I. Once a product is registered, First PSUR should be submitted with period covering 1 year from date of registration of the product in Bangladesh.

II. Then every 2 years for next 4 years.

III. PSUR after five years will be on ad hoc if DGDA requires.

IV. Each PSUR should cover the period of time since the last updated report and must be submitted within 90 calendar days (for PSUR covering up to 12 months) or 120 calendar days (for PSUR covering more than 12 months) from the data lock point.

Wherever there is Global PSUR available with the MAHs, which may or may not fit the exact local interval as mentioned above, an addendum statement/summary can be accepted to cover the gap period between Global PSUR and local interval, i.e., submission of Global PSUR along with addendum statement to meet local or country requirement.

VI. MODULE SIX: PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)

A. Introduction

While a pharmacovigilance system is a system used by MAH to fulfil its pharmacovigilance tasks and responsibilities designed to monitor registered products' safety and any changes to their benefit-risk balance, the Pharmacovigilance System Master File (PSMF) is a detailed description of the system used. This part provides detailed guidance regarding the requirements for the PSMF in Bangladesh, including its maintenance, content and associated submissions to the Authority.

Since PSMF provides detailed description of the pharmacovigilance system within a MAH, it reflects the MAH's readiness and competency in pharmacovigilance. The PSMF could also provide general insights on the pharmacovigilance system of the MAH to the Authority. A MAH may be required to submit PSMF to the Authority in circumstances whereby an assessment of its pharmacovigilance system is warranted such as prior to a Good Pharmacovigilance Practice Inspection (GVPI) and as per requirement of DGDA.

B. Structures and Processes

I. The PSMF is applicable for any human medicinal product registered in Bangladesh, irrespective of the product registration procedure or marketing status (except for cosmetic product and veterinary product).

II. The content of the PSMF should mainly contain details of Bangladesh pharmacovigilance activities and local availability of safety information for medicinal products registered in Bangladesh. Regional and /or global information or activities should only be included when necessary to reflect the overall pharmacovigilance system of the MAH.

C. Submission and Maintenance of PSMF

I. All MAHs are required to prepare PSMF as per Annex IV However, submissions of PSMF to the Authority are applicable only to MAHs involved in GVPI and the timeline of submission will be notified by the DGDA. Under this scenario, maintenance and submission of the updated PSMF is applicable.

II. The PSMF is expected to be submitted only once for each MAH, unless requested by the Authority. Submission of PSMF should be in hardcopy.

III. As the PSMF content will continue to be updated from time to time, all changes should be recorded. However, any changes in these situations require a notification to be submitted to the ADRM cell:

- changes in QPPV, and the back-up personnel contact details;
- changes in PV safety database (e.g. data migration);
- changes in significant service provider, especially concerning the reporting of safety data;
- organizational changes, such as takeovers, mergers impacting structure and responsibilities of PV function.

Note: Timeline to notify ADRM cell is within 30 calendar days from the effective date of changes or after first knowledge by MAH.

D. Content of the PSMF

The content of the PSMF should be followed according to the below listed primary topic sections and contain fundamental information to describe the pharmacovigilance system.

1. Qualified Person for PV (QPPV), QPPV back-up

I. The information relating to the QPPV, QPPV back-up shall include:

- A summary curriculum vitae with the key information on the role of the QPPV, and their respective back-up;
- Contact details (including position in company, address, telephone number, fax number, emergency contact number and email address);
- Details of back-up arrangements to apply in the absence of the QPPV.

II. If the QPPV, and the respective back-up is provided by a third party (contract), the name of the company the person works for should also be provided.

III. A list of tasks that have been delegated by the QPPV shall be included. The list should outline the activities that are delegated, to whom and the accessibility to a medically qualified person if applicable.

2. Organizational Structure of the MAH

I. The content of the PSMF should mainly contain details of pharmacovigilance activities

II. This section should provide a description of the organisational structure of the MAH relevant to the pharmacovigilance system. A clear overview of the company(s) involved (including third parties), the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfillment of pharmacovigilance obligations is expected.

III. The organisational structure should be showing the position of the in the organisation. Diagrams may be particularly useful with the name of the department or third party clearly indicated.

IV. The organisational structure should be able to reflect the site(s) where the pharmacovigilance functions are undertaken, including but not limited to individual case safety report collection, evaluation, safety database case entry, PSUR production, RMP management with regards to safety issues as well as management of safety variations to products whichever related.

V. The description of organisational structure should clearly list down system/database/vendors (third parties) that are involve in Pharmacovigilance system/activities and system/database/vendors (third parties) that contribute to and/or interfere with the local Pharmacovigilance system/activities. This may be in the form of a list or table to show the parties involved, the roles undertaken and the concerned product(s).

VI. The delegated pharmacovigilance activities should also be described in this section, including arrangements with other parties to reflect the company's overall/whole picture of the pharmacovigilance system in Bangladesh.

VII. Links with other organisations, such as co-marketing agreements and engagement of a third party on pharmacovigilance activities should be outlined.

This may be shown in a list or table on the parties involved, the roles undertaken and the concerned product(s). The list or table can be organized according to:

- Service providers (e.g. medical information, auditors, patient support programme providers and etc.);
- Commercial arrangements (distributors, licensing partners, co-marketing and etc.);
- Other technical providers (hosting of computer system and etc.)

3. Sources of Safety Data

I. This section should describe the safety data collection process, including all parties responsible, for solicited and spontaneous case collection for products registered in Bangladesh. This should include medical information sites (e.g. company sponsored or owned websites/any mass media) as well as affiliate offices and contractual parties.

II. The focus should be on activities in Bangladesh. However, global information or global activities may be elaborated if deemed necessary.

4. Computerized Systems and Databases

I. This section should describe the location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose. The computerised system that should be described includes all computerised system and database that are used in performing all PV activities and especially those related to the source of safety data.

II. If the computerised system is not applicable, a paper-based system may be used. The paper-based system must be able to reflect a systematic approach of managing the safety information.

III. The management of data, mechanisms used to assure the integrity, change control, validation status of key aspects of system functionality, back-up procedure and accessibility of the safety data to collate information about AE should be described.

5. Pharmacovigilance Processes

I. This section describes the overview of pharmacovigilance process (e.g. standard operating procedures, manuals in Bangladesh and/or global level), data handling (e.g. the type of ICSR retained) and records (e.g. safety database and paper file) for the performance of a pharmacovigilance system.

II. The list should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

III. The details required shall be including, but not limited to:

List of SOP:

- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities (if applicable);
- PSUR scheduling, production and submission (if applicable);
- Implementation of safety updates to the label, package insert (PI)
- Risk management system and monitoring of the outcome of risk minimisation measures (if applicable)
- Communication of safety concerns to consumers, healthcare professionals and the Health authorities;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets;

6. Pharmacovigilance System Performance

The pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file should include a description of the monitoring methods applied and contain as a minimum:

- ICSR Submission timeline should be monitor (e.g. figures/graphs/summary of submission).

- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance.
- An overview of the timeliness of PSUR reporting to DGDA in Bangladesh.

7. Quality System

I. This section describes the quality management to the organisational structure and pharmacovigilance system. This shall include:

- **Document and record archive-** Provide a description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF, as well as other pharmacovigilance records and documents;
- **Procedural documents-** The control, accessibility, implementation and maintenance of documents (e.g. standards, operating procedures, work instructions and etc.) used in pharmacovigilance should be described. The applicability of the various documents at global, regional or local level within the organisation or under control of third parties should be clearly stated;
- **Training-** All personnel involved in the pharmacovigilance activities shall receive initial and continued training. This training shall relate to the roles and responsibilities of the personnel. Adequate training should also be considered by the organisation for staff members with no specific pharmacovigilance tasks and responsibilities assigned to them but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance (e.g. telephone operators, receptionists, etc.). Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs and legal affairs. The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.
- **Auditing-** Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. 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. The audit report must be documented into the quality system.

8. Annexure to the PSMF

- List of medicinal products covered by the pharmacovigilance system
  - A list of products registered under Biologic category;
  - A list of products with special condition for registration;
  - A list of products listed under current National Immunisation Programme (NIP);
- A list of contractual agreements covering delegated activities including the medicinal products and territory(ies)
- A list of tasks that have been delegated by the qualified person for pharmacovigilance
- A list of all completed audits, for a period of five years, and a list of audit schedules

VII. MODULE SEVEN: PHARMACOVIGILANCE INSPECTIONS

A. Introduction

This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the Bangladesh and outlines the role of the different parties involved.

In order to determine that marketing authorisation holders comply with GVP obligations, DGDA has such authority to conduct the following inspections:

a) System and product-related inspections

b) Routine and "for cause" pharmacovigilance inspections

c) Pre and Post-Authorization inspection (as required)

The objectives of pharmacovigilance inspections are:

I. to determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;

II. to identify, record and address non-compliance which may pose a risk to public health;

III. to use the inspection results as a basis for enforcement action, where considered necessary

B. Structures and processes

1. Inspection types

a) System and product-related inspections

Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system. Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

b) Routine and "for cause" pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

For cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger.

c) Pre and Post-Authorisation inspection

Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorisation application.

Principles and procedures for requesting pre-authorisation inspections should be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorisation.

Post-authorisation pharmacovigilance inspections are inspections performed after a marketing authorisation is granted and are intended to examine whether the marketing authorisation holder complies with its pharmacovigilance obligations.

2. Inspection planning

Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

3. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by competent authorities and whether it is a system or product-related inspection

The following elements should be considered when preparing the scope of the inspection, as applicable:

- information supplied in the pharmacovigilance system master file;
- information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency and data quality audits;
- specific triggers

It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

a) Routine pharmacovigilance inspections

Routine pharmacovigilance inspections should examine compliance with national legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:

- individual case safety reports (ICSRs):
  - collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed to fulfil marketing authorisation holder's pharmacovigilance obligations and departments other than drug safety;
  - assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality.
  - follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
  - 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 for ICSRs;
- periodic safety update reports (PSURs):
  - completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;

- addressing safety topics, providing relevant analyses and actions;
- formatting according to requirements;
- timeliness of submissions;

- 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, e.g. the implementation of recommendations following data review;
  - implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
  - timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
  - implementation of approved changes to safety communications and product information, including internal distribution and external publication;
- interventional (where appropriate) and non-interventional clinical trials:
  - reporting suspected unexpected serious adverse reactions (SUSARs)
  - receiving, recording and assessing cases from interventional and non-interventional trials
  - submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP 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:
  - QPPV roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
  - 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.

The inspection may include the system for the fulfilment of conditions of a marketing authorisation and the implementation of risk–minimisation activities, as they relate to any of the above safety topics.

b) For cause inspections

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed and below, may be relevant:

- QPPV involvement and awareness of product-specific issues;
- in-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

4. Inspection process

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented.

The procedures on pharmacovigilance inspections cover, at least, the following processes:

- sharing of information;
- inspection planning;
- pre-authorisation inspections;
- coordination of pharmacovigilance inspections in the Bangladesh;
- preparation of pharmacovigilance inspections;
- conduct of pharmacovigilance inspections;
- reporting of pharmacovigilance inspections and inspection follow-up;
- communication and prioritisation of pharmacovigilance inspections and findings;
- record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
- unannounced inspections;
- sanctions and enforcement in case of serious non-compliance;
- recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

5. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed.

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections.

6. Regulatory actions and sanctions

In order to protect public health, competent authorities are obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action.

In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- education and facilitation: national competent authorities may communicate with marketing authorisation holder representatives (e.g. in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorisation holder's proposals for corrective and preventive actions;

- provision of information to other competent authorities, the Agency or third country regulators under the framework of confidentiality arrangements;
- inspection: non-compliant marketing authorisation holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which competent authorities may issue stating the legislation and guideline that has been breached, reminding marketing authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- DGDA may consider making public a list of marketing authorisation holders found to be seriously or persistently non-compliant;
- actions against a marketing authorisation(s) or authorisation application(s) e.g.
    - Urgent Safety Restriction;
    - variation of the marketing authorisation;
    - suspension or revocation of the marketing authorisation;
    - delays in approvals of new marketing authorisation applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorisations;
    - requests for pre-authorisation inspections;
- product recalls e.g. where important safety warnings have been omitted from product information;
- action relating to marketing or advertising information;
- amendments or suspension of clinical trials due to product-specific safety issues;
- administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

7. Qualification and training of inspectors

Inspectors who are involved in the conduct of pharmacovigilance inspections, appointed by, the the national competent authority in accordance with national regulation and follow the provisions of the national competent authority.

The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections. They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of the concerned competent authority.

8. Quality management of pharmacovigilance inspection process

Quality of the pharmacovigilance inspection process is managed by DGDA and covered by their pharmacovigilance systems and associated quality systems, meaning that the process is also subject to audit.

Quality and consistency of the inspections is facilitated by the procedures for pharmacovigilance inspections.

a) Role of DGDA

National competent authority should establish the legal and administrative framework within which pharmacovigilance inspections operate, including the definition of the rights of inspectors for inspecting pharmacovigilance sites and access to pharmacovigilance data.

National competent authority should provide sufficient resources and appoint adequately qualified inspectors to ensure effective determination of compliance with good pharmacovigilance practice. The inspector(s) appointed may be accompanied, when needed, by expert(s) on relevant areas.

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures.

The scheduling and conduct of these inspections will be driven by the preparation of inspection programmes based on a systematic and risk-based approach.

As a general approach, a marketing authorisation holder should be inspected on the basis of risk-based considerations, but at least once every 5 years.

b) Role of marketing authorisation holders and applicants

I. always to be inspection-ready as inspections may be unannounced;

II. to maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request,

III. to ensure that the sites selected for inspection, which may include firms employed by the marketing authorisation holder to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;

IV. to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;

V. to ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;

VI. to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

VIII. MODULE EIGHT: MISCELLANEOUS

A. EMERGING SAFETY ISSUES

Safety issues considered by a MAH to require urgent attention by the Authority because of the potential major impact on the safety or risk-benefit balance of the product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals. Examples include but are not limited to:

I. Safety-related actions by regulatory agencies in reference countries or Regulatory bodies such as:

- The withdrawal or suspension of the medicine's availability (except for solely business decisions);
- The addition or modification of a contraindication, warning or precaution statement to the product information or label for safety reasons;
- The modification or removal, of an indication for safety reasons.

II. Changes in the nature, severity or frequency of known serious adverse events.

III. Detection of new risk factors for the development of a known adverse reaction or a new adverse reaction that may impact on the safety or benefit-risk balance of the medicine.

IV. An unusual and significant lack of efficacy occurring in or outside Bangladesh that may have implications for public health.

V. Major safety findings from a completed non-clinical study, post-registration study or clinical trial that may impact the safety or risk-benefit balance of the medicine.

VI. A signal of a possible teratogenic effect or of significant hazard to public health.

The examples above are not intended to be an exhaustive list of emerging safety issues, and it is up to MAH to assess safety issues on a case-by-case basis and evaluate whether this has an impact on the medicine's safety or risk-benefit balance and/or implications for public health.

All pertinent factors should be taken into account when assessing a safety issue. Issues to consider include the medicine, the risks involved and the regulatory context. If the MAH determines after the appropriate assessment that a safety issue is not an emerging safety issue and do not report it, the MAH should document a justification for this decision.

This documentation may be requested by the Authority at any time. If in doubt about a safety issue, treat it as an emerging safety issue.

A safety issue leading to regulatory action in FDA, TGA, MHRA and EMA should be reported to the Authority regardless of whether the MAH agrees with their recommendations and conclusions.

These safety issues, which may affect the safety or benefit-risk balance of a medicinal product, are not to be submitted as individual case reports. They should be notified in writing to the Authority as Emerging Safety Issues. Generally, emerging safety issues should be notified to the Authority upon knowledge of the MAH. Only actions that have taken place need to be notified to the Authority, not actions that are being contemplated.

This written notice should indicate the points of concern and the actions proposed in relation to authorization for the concerned product. Those safety issues should also be analyzed in the relevant sections of the PSUR of the registered product.

B. SAFETY EVALUATION BY THE PHARMACOVIGILANCE SECTION

As part of the safety evaluation process, ADRM Cell, DGDA may request additional safety documents from the MAH to assist the evaluation. MAH will be notified the safety issues warrant and any regulatory action (e.g. product information update) by DGDA.

C. SAFETY COMMUNICATION

Communication tools and channels have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations.

1. Direct Healthcare Professional Communication (DHPC)

A Direct Healthcare Professional Communication (DHPC) is a communication intervention by which important safety information is delivered directly to individual healthcare professionals by MAH or the Authority (in special cases), to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

DHPCs are not intended to be used as:

I. Replies to inquiries from healthcare professionals;

II. Communication tools to inform healthcare professionals on any misinformation in the PI due to errors made by the MAH;

III. As educational materials for routine risk minimization activities;

IV. A platform to announce a new product launch.

The MAH must ensure that it has an appropriate system of pharmacovigilance and risk management to assure responsibility and liability for marketed medicines and to ensure appropriate action can be taken when necessary.

Situations where a DHPC can be considered as part of the risk management process include: suspension, withdrawal; revocation of product registration with recall of the medicine from the market for safety reasons; important changes to the package insert (e.g. new warnings or contraindications, reduced recommended dose, or restricted indications or availability); or a change in the balance of benefits and risks for a medicine.

To distribute a DHPC in Bangladesh, the MAH should submit a draft communication plan to the Authority for approval that includes:

I. Objective;

II. Scheduled timeline proposed;

III. Recipients;

IV. Dissemination method;

V. Current approved package insert with changes clearly marked/highlighted;

VI. Other related communications and post-communication strategy.

The appended Template for Direct Healthcare Professional Communication should comply to format (see Annex V).

Further recommendations on DHPC:

I. Safety information should be clear and concise; it should not exceed three (3) pages if possible;

II. The reason for dissemination should be explained (e.g. availability of new data);

III. Recommendations to healthcare professionals should be given on how to minimize risk, if known and information for the general public;

IV. The safety concern should be placed in the context of the overall benefit of treatment.

The distribution of a proposed package insert with highlighted changes should be informed and agreed with the Authority prior to circulation.

Once the DHPC has been finalized, the MAH should submit to the Authority the final signed DHPC before it could be distributed to the recipients accordingly. Notification to the Authority should be submitted upon completion of distribution (within the proposed timeline) to complete the process of DHPC communication.

D. Boxed Warning

The concept of boxed warning is intended to highlight life-threatening or serious and/or unexpected adverse events. This shall be succinct and designed to draw the prescriber's attention to detailed information within the main text of the package insert.

This must be separated and highlighted from the other text in the package insert, typically characterized by a black box border and normally placed in the first section of the package insert.

A boxed warning is ordinarily used to highlight the following situations to prescribers:

I. There is an adverse reaction so serious compared to the potential benefit from the drug (e.g. fatal, life-threatening, or permanently disabling) whereby it is essential that the adverse reaction be considered in assessing the risks and benefits of using the drug;

II. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug such as:

- Patient selection;
- Careful monitoring;
- Avoiding certain concomitant therapy;
- Addition of another drug;
- Managing patients in a specific manner;
- Avoiding use in a specific clinical situation.

III. Drug approval within restrictions to ensure safe use because it is concluded that the drug can be safely used only if distribution or use is restricted;

IV. Certain especially important information, e.g. under Warnings and Precautions and Contraindications sections;

V. In some cases, a boxed warning may be based on expected/anticipated adverse events, though normally based on observed serious adverse events;

VI. The drug has important risk/benefit information that is unique/specific to that drug only in its drug class;

VII. Serious or life-threatening drug interactions.

The boxed warning provides a brief, concise summary of the information that is critical for prescriber to be aware of, including any restriction on distribution or use. If there is more detailed discussion of the concerned matter in either Contraindications or Warnings and Precautions section or in any other labelling section that contains pertinent information, a cross reference to that section must be provided (e.g. see Warnings and Precautions).

There may be a valid reason for the use of boxed warning on the package insert and it will be discussed on a case-by-case basis.

E. Post-market surveillance for Medical Device

MAH should play an active role during the post-market phase by systematically and actively gathering information from post-market experience with their devices in order to update their technical documentation and cooperate with the national competent authorities in charge of vigilance and market surveillance activities. To this end, manufacturers should establish a comprehensive post-market surveillance system, set up under their quality management system and based on a post-market surveillance plan. Relevant data and information gathered through post-market surveillance, as well as lessons learned from any implemented preventive and/or corrective actions, should be used to update any relevant part of technical documentation, such as those relating to risk assessment and clinical evaluation, and should also serve the purpose of transparency.

For the purposes of this Regulation, the following definitions apply:

Medical Device Adverse Event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether related or not related to the medical device in Bangladesh.

According to WHO, A medical device can be any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination for a medical purpose.

Accessory to a medical device: An article intended specifically by its manufacturer to be used together with a particular medical device to enable or assist that device to be used in accordance with its intended use."

Active medical device: Any medical device, operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patients, without any significant change, are not considered to be active medical devices. Standalone software that fulfills the attributes of the definition of "medical device" above is deemed to be an active medical device. (eg. ECG Machine)

Active therapeutic device: Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap. (eg. Heart Valve)

Active device intended for diagnosis: Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or to support in treating physiological conditions, states of health, illnesses or congenital deformities. (eg. X-ray Machine, Ultrasonography Machine)

Explanation for Combination Products:

- Cross-labelled to medicinal products, when the medicinal product and the medical device are packaged separately but cross-referenced in their respective labelling as intended to be used only in combination.
- Medical device components/parts assembled to single integral products where the medical device part is used to administer the medicinal product and is marketed as a single integral entity with the medicinal product intended exclusively for use in the given combination and is not reusable, e.g., Pre-filled syringe

In Vitro Diagnostic (IVD) Medical Device: A medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

Post-Marketing Surveillance and Adverse Event (Vigilance) Reporting:

Once a medical device is placed on the market in Bangladesh, the MAH shall adhere to requirements of post-marketing surveillance (PMS) to systematically monitor the performance of the device during use in Bangladesh. Adverse events should be analyzed and reported to a designated authority in DGDA.

As part of the Manufacturer's Quality management System, appropriate corrective and preventive actions may be applied to prevent or reduce the likelihood of the recurrence of adverse events. Medical device MAH should submit such vigilance reports within 30 calendar days of manufacture received date for Non . Serious and 15 Calendar days for serious report.

Definitions

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this.

An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse event following immunization (AEFI)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse reaction

A response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Use outside the marketing authorization includes off-label use, overdose, misuse, abuse and medication errors.

Audit

A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled

Biologics / Biological medicinal product

A medicinal product, the active substance of which is a biological substance .

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Biosimilar medicinal product

A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal) product, and which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

Compassionate use of a medicinal product

Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life- threatening, and who cannot be treated satisfactorily by registered medicinal product.

Company core data sheet (CCDS)

For medicinal products, a document prepared by the marketing authorization holder containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product

Consumer

For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative of a patient or carer.

Data lock point

For a Periodic Benefit-Risk Evaluation Report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date or the date of registration approval.

Direct healthcare professional communication (DHPC)

A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

DHPCs are not replies to enquiries from healthcare professionals.

Emerging safety issue

A safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals

Falsified medicinal product

This relates to any medicinal product with a false representation of:

- its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

- its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or
- its history, including the records and documents relating to the distribution channels used. This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

Healthcare professional

For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and other allied healthcare professionals.

ICSR

This refers to the format and content for the submission of an individual report of suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time.

A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect medicinal product.

Identified risks

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest

Medication error

This is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization.

Occupational exposure

This refers to the exposure to a medicinal, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as a finished product.

Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information.

When applying this definition, clinical judgement should always be applied.

Potential risks

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed

Risk management plan (RMP)

A detailed description of the risk management.

The risk management plan established by the marketing authorization holder shall contain the following elements: (a) an identification or characterization of the safety profile of the medicinal product(s) concerned; (b) an indication of how to characterize further the safety profile of the medicinal product(s) concerned; (c) a documentation of measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) a documentation of post-authorization obligations that have been imposed as a condition of the marketing authorization

Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions

Risk minimization measure/ Risk minimization activity

Interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur

Safety concern

An important identified risk, important potential risk or missing information.

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect

Medical device

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

Medication error

An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient

International Birth Date (IBD)

The date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world

Reference safety information

In periodic benefit-risk evaluation reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where it markets the product, except when the local regulatory authority specifically requires a modification

Post-authorisation safety study (PASS)

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management. A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design

Pharmacovigilance system master file (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products

Pharmacovigilance

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem .

In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable EU legislation for are:

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Periodic safety update report (PSUR)

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.

Package leaflet

A leaflet containing information for the user which accompanies the medicinal product

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

Solicited sources of individual case safety reports

Organized data collection systems, which include clinical trials, registries, post-authorization named patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance. For the purpose of safety reporting, solicited reports should not be considered spontaneous but classified as individual case safety reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or the marketing authorization holder

Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics

IX. ACRONYMS

ADE	Adverse Drug Events
ADR	Adverse DrugReaction
ADRM	Adverse Drug Reaction Monitoring
AE	Adverse Events
AEFI	Adverse Events Following Immunization
CIOMS	Council for International Organizations of Medical Sciences
DGDA	Directorate General of DrugAdministration
DHPC	Direct Healthcare Professional Communication
EMA	European Medicine Agency
GVP	Good Pharmacovigilance Practice
ICH	International Conference on Harmonization
ICSR	Individual CaseSafety Report
MAH	Marketing Authorization Holder
MOHFW	Ministry of Health and Family Welfare
PQC	Product Quality Complaints
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
QPPV	Qualified Person forPharmacovigilance
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
WHO	World Health Organization

A. Annex I: Suspected Adverse Event Reporting Form

Yellow Card

SUSPECTED ADVERSE EVENT REPORTING FORM

Identities of reporter, patient, institution, and product trade name(s) will remain confidential

* Mandatory Information

FOR OFFICE USE ONLY

AE report number _____ Data received _____

A. PATIENT INFORMATION

Name/Initial:
Address:

* Contact number

*Age--------- Weight(Kg)------- *Gender ☐Male ☐Female ☐Other

Pregnant : ☐ Yes ☐ No ☐Unknown ☐Not applicable

B. SUSPECTED ADVERSE EVENT INFORMATION

Type of event:

☐ Adverse drug reaction/AEFI
☐ Product quality problem
☐ Medication error
☐ Others (Please specify)

***Describe event including relevant tests and laboratory results:**

***Event start Date** _____

***Event stopped Date** _____

Was the adverse event treated? ☐ **Yes** ☐ **No**

If yes, please specify:

Action taken after reaction:

☐Dose stopped
☐Dose reduced
☐No action taken

Did reaction subside after stopping / reducing the dose of the suspected product? ☐ Yes ☐ No ☐ Not applicable

Did reaction appear after reintroducing the suspected product? ☐ Yes ☐ No ☐ Not applicable

Seriousness of the adverse event:

☐ Non serious
☐ Serious
- ○ Hospitalization or prolongation of hospitalization
- ○ Disability or permanent damage
- ○ Congenital anomaly/birth defect
- ○ Life threatening
- ○ Death

***Outcomes attributed to the adverse event:**

☐ Recovered
☐ Recovered/resolved with sequela
☐ Not recovered
☐ Unknown
☐ Fatal (date of death: _____)

Other relevant history: (pre-existing medical history)

☐ Hypersensitivity ☐ Allergies ☐ Hypertension ☐ Liver or kidney problems ☐ Smoking ☐ Alcohol ☐ Diabetes

☐ Others (Please specify):

C. SUSPECTED DRUG/VACCINE INFORMATION

Brand/Trade name _____ *Generic name with strength _____

*Indication _____

*Medication Start Date/Vaccination Date _____ End Date/Vaccination Time _____

Dosage Form _____ *Frequency (Daily Dose) _____ Batch/Lot number _____

Manufacturer _____ Diluent Information for vaccine _____

CONCOMITANT MEDICINE/VACCINE INFORMATION

Brand/Trade name	Generic name	Indication	Dosage form	Strength & Frequency

Page 1 of 2 **P.T.O**

D. REPORTER INFORMATION

*Name & Address _____

_____

Email address _____ *Mobile phone _____

Occupation _____ *Signature

*Date of this report submission _____

Evaluation/Review Committee Comments:

ADRM Cell	TSC	ADRAC

General instructions for completing the form:

- Detailed information about each field can be found in the instructions available in the DGDA website. (www.dgda.gov.bd).
- Fill in as much information as possible. Do not leave anything blank. If unknown, write "unknown" or "n/a" if not applicable.

What to report:

- Adverse drug reactions/AEFI
- Unknown or unexpected ADRs/AEFI
- All suspected reactions to new drugs/vaccines
- Unexpected therapeutic effects
- All suspected drug/vaccine interactions
- Product quality problems
- Medication/vaccination errors

How to fill and submit the report :

ADE/AEFI reports can be submitted through online in the DGDA website (www.dgda.gov.bd)

Hard copy of Yellow Card can also be filled and sent to the ADRM Cell by (i) email (adrmcell.dgda@gmail.com or (ii) post. In emergency cases or when forms are not readily available, it can be notified to the ADRM cell by phone.

N.B: Additional Page can be used for detailed information if needed

ঔষধ ব্যবহারকারীদের নির্দেশনাঃ

১। নিবন্ধনকৃত চিকিৎসকের ব্যবস্থাপত্র অনুযায়ী সঠিক মাত্রায়, সঠিক পদ্ধতিতে পূর্ণকোর্স এন্টিবায়োটিক ব্যবহার করুন।

২। কোন ঔষধ ব্যবহারে বিরূপ প্রতিক্রিয়া দেখা দিলে ঔষধ প্রশাসন অধিদপ্তরকে অবহিত করুন।

Postal Address:	Contact Information:
ADRM Cell, Pharmacovigilance Department Directorate General of Drug Administration Aushad Bhavan, Mohakhali Dhaka-1212, Bangladesh	Tel: 02222-280803 Cell No.: +8801728-349503 E-mail: adrmcell.dgda@gmail.com

Version 03

B. Annex II: Bangladesh -Specific Annex for RMP

TEMPLATE FOR RISK MANAGEMENT PLAN (RMP)
BANGLADESH- SPECIFIC ANNEX (BSA)

I. Product Overview in Bangladesh

Date of Submission	DD/MM/YYYY
BSA Version Numbe r	Current BSA version number eg. V1
Product Name	
Active Ingredient(s)	
Dosage Form	
DAR Number	
Date of First Registration Approval in Bangladesh	
Product Category	e.g. New drug products /Biologics /Others
Marketing Authorization Holder (MAH)	
Details of QPPV(name, designation, email, telephone number)	
Approved Indication(s)	

II. Changes from Previous RMP Version

Brief summary of significant safety-related changes from the previous RMP submission.

This section may not be applicable for the first RMP submitted post-registration

III. Summary of Changes to the BSA Over Time

Brief tabulated summary of safety-related changes to the BSA over time.

<Suggested format>

Date of Submission	BSA Version Number	Description of Change
DD/MM/YYYY	V1	First BSA submitted post-registration
DD/MM/YYYY	V2	

IV. Safety Specification: Summary of Safety Concerns

To list the safety concerns in relation to the approved indication(s) in Bangladesh.

<Suggested format>

Important identified risks	Heart failure
Important potential risks	Liver injury Peripheral neuropathy
Missing information	Bone fracture

V. Pharmacovigilance Plan

To describe the pharmacovigilance activities (routine and/or additional), relevant to the Bangladesh context, that are planned or carried out to address the safety concerns.

Routine pharmacovigilance activities are required for all products.

If no additional pharmacovigilance activities are deemed necessary, it should be indicated as 'nil'.

a. Routine Pharmacovigilance Activities

To describe routine activities that are planned or carried out in Bangladesh.

b. Additional Pharmacovigilance Activities by Safety Concern

<Suggested format>

Safety Concerns	Pharmacovigilance Activities	Additional Information
Important identified risks • Heart failure	Additional: PASS [study title]	
Important potential risks • Liver injury • Peripheral neuropathy	Additional: Nil	
	Additional: Nil	
Missing information • Bone fracture	Additional: Nil	

VI. Risk Minimization Plan

To describe the risk minimization activities/measures (routine and/or additional), relevant to the Bangladesh context, that are planned or carried out to address the safety concerns.

Routine risk minimization activities are required for all products.

If no additional risk minimization activities are deemed necessary, it should be indicated as 'nil'.

a. Routine/Additional Risk Minimization Activities by Safety Concern

<Suggested format>

Safety Concerns	Risk Minimization Activities	Additional Information
Important identified risks • Heart failure	Routine: Prescription-only medicine; Labelling in local PI: 'Section XX Special warnings and precautions for use' and 'Section XX. Undesirable effects'; Labelling in Packaging Leaflet: 'Before you start to use it' and 'Side effects'. Additional: DHPC letter & educational materials	
Important potential risks • Liver injury • Peripheral neuropathy	Routine: Prescription-only medicine; Labelling in local PI: 'Section XX Special warnings and precautions for use' and 'Section XX. Undesirable effects'; Labelling in Packaging Leaflet: 'Before you start to use it' and 'Side effects'. Additional: educational materials	
Missing information • Bone fracture	Routine: Nil Additional: Nil	

VII. Additional Information

To list the RMP documents enclosed in this submission and to provide other comments (if applicable).

If the additional risk minimization activity includes a Patient Alert/Reminder Card, the following information are required:

Patient Alert/Reminder Card Checklist

- Product name and Active Ingredient
- Dosage form
- Introduction

This patient alert/reminder card contains important safety information that you need to be aware of before, during, and after treatment with Product Name.

Show this card to any doctor, pharmacist, dentist or other healthcare professional involved in your treatment.

- Content Information

To be aligned with latest approved package insert.

- Warding and Contraindication
  - When to seek immediate attention
  - Contraindication
  - Information on pregnancy

- Additional Advice

Please make sure you also have a list of all your other medicines with you at any visit to a doctor/ pharmacist.

Keep this card for 'X number' months after treatment is completed since side effects may occur after your last dose.

- Treatment details
- ADR reporting

If you notice any side effects, talk to your doctor or pharmacist. You may report any adverse drug reactions directly to the National Regulatory Authority at the official website

- Additional information (for biologic/biosimilar products only):

All ADR reports for biologics/biosimilar should include Brand name, active ingredient, and batch number for traceability purposes.

- Version and month & year of update

C. Annex III: Bangladesh Specific (BSA) for PSUR

<Cover Page>

NAME OF THE MEDICINAL PRODUCT(S) COVERED

INTERNATIONAL BIRTH DATE (IBD): <Date>

BANGLADESH REGISTRATION DATE (BBD): <Date>

DATE OF SUBMISSION: <Date>

INTERVAL COVERED BY THIS REPORT:

From <date> to <date (i.e. data lock point)>

DATE OF THIS REPORT:

<Date>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

<E-mail address> (contact person for the PSUR procedure)

NAME AND CONTACT DETAILS OF QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>

<PSUR Content >

I. Product Overview in Bangladesh

Submission Number (PBRER Cover Period)	e.g. First submission (DD/MM/YYYY – DD/MM/YYYY)
Product Name	
Active Ingredient(s)	
Dosage Form	
MAH/DAR No	
Product Category	e.g. New drug product/ Biologics/Others

II. Summary of Safety Changes

a. Actions Taken in the Reporting Interval for Safety Reasons

Brief tabulated summary of significant actions related to safety that have been taken in any countries during the reporting interval, relating to marketing experience by the MAH, or authorities.

<Suggested format>

Action(s) taken by	Description of the action(s) taken	Status of the action(s) taken
US FDA	MAH was requested to include liver injury in the Warnings and Precautions section of the US PI.	Updated US PI was approved on DD/MM/YYYY

b. Changes in Reference Safety Information (RSI)

Brief tabulated summary of changes in RSI during the reporting interval.

<Suggested format>

Version (Date)	Description of changes	Applicable to Bangladesh (Yes/No)
3.0 (DD/MM/YYY	Update to the Warnings and Precautions section regarding the risk of heart failure	Yes

c. Action(s) Taken or Planned in Bangladesh

State whether or not a specific action has been taken or is planned for Bangladesh, pertaining to the actions taken or RSI changes listed above in II(a) and II(b). If any actions are taken in Bangladesh, the status of the actions should be listed.

<Suggested format>

Type of action/plan	Details
Safety-related	
Non safety-related	

III. List of Signals Evaluated

To list all signals that were closed (e.g. the evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation, at the end of reporting interval.

The description(s) of the signal evaluations are not to be included.

D. Annex IV: Template for Pharmacovigilance System Master File (PSMF)

Pharmacovigilance System Master File (PSMF)

Version No XX

Date of Preparation: DD MM YYYY

Date of Last Update: DD MM YYYY

Marketing Authorization Holder (MAH): XXX XXX

Contents

E. Annex V: Direct Healthcare Professional Communication (DHPC)

<Date>

<Active substance, name of medicinal product and main message (e.g. introduction of a warning or a contraindication)>

Dear Healthcare professional,

<Name of MAH> in agreement with <Name of the health Authority> would like to inform you of the following:

Summary

Guidance: This section should be in bold/larger font size than the other sections of the DHPC and preferably in bullet points.

- <Brief description of the safety concern in the context of the therapeutic indication, recommendations for risk minimization (e.g. contraindications, warnings, precautions of use) and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

Background on the safety concern

Guidance: This section may include the following information:

- <Brief description of the therapeutic indication of the medicinal product>
- <Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamics mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors)>
- <An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>
- <A statement indicating any association between the adverse reaction and off-label use, if applicable>
- <If applicable, details on the recommendations for risk minimization>
- <A statement if the product information is to be or has been revised, including a description of the changes made or proposed>

Guidance: No need however to include or attach the precise (translated) text of the product information which, at the time of dissemination of the DHPC may not be available as final approved translations)

- <Place of the risk in the context of the benefit>
- <The reason for disseminating the DHPC at this point in time>
- <Any evidence supporting the recommendation (e.g. include citation(s) of key study/ies)>
- <A statement on any previous DHPCs related to the current safety concern that have recently been disseminated>
- <Any schedule for follow-up action(s) by the marketing authorization holder/competent authority, if applicable>

Call for reporting

- <A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>
- <For biological medicinal products, also include a reminder to report the product name and batch details>.
- <Mention if product is subject to additional monitoring and the reason why>

Company contact point

- <Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes (if applicable)

- <Link/reference to other available relevant information, such as information on the website of a competent authority>
- <Additional scientific information, if applicable>
- <List of literature references, if applicable>

F. Annex Vi: Medical Device Adverse Event Reporting Form

SUSPECTED ADVERSE EVENT REPORTING FORM FOR MEDICAL DEVICES

Identities of reporter, patient, institution, and product trade name(s) will remain confidential

I – GENERAL INFORMATION				
DGDA Adverse Event Reference No.				
Product Owner Reference No.				
Report Type *(please select one)*	☐ Initial ☐ Follow-up ☐ Final ☐ Trend			
AE Category *(please select one)*	☐ Serious Public Health Threat ☐ Death ☐ Serious Deterioration in State of Health ☐ Others			
Date of Adverse Event *(dd/mm/yyyy)*				
Date Company aware *(dd/mm/yyyy)*				
II – PARTICULARS OF REPORTING COMPANY				
Name of company				
Company address				
Contact person name				
Designation				
Tel no.				
Email Address				
III – DEVICE DETAILS				
Device Name				
Usage of Device/Intended Purpose				
Device Regulatory Status (e.g. SMDR Listing No. if device is registered)				
Catalogue No.				
Model No.				
Lot/Batch No.				
Serial No.				
Software version				
Accessories/Associated Devices affected (if any)				
GMDN Code				
GMDN Term				
Product Owner Name				
Product Owner Address				
IV – DESCRIPTION OF EVENT				
Device Operator *(please select one)*	☐ Physician ☐ Patient ☐ Others (Please specify:) ☐ None or problem noted prior to use			
Device disposition/current location				
Description of Event or Problem (including any patient follow up as a result of the event/problem)				
Frequency of Occurrence of Similar Adverse Events Globally in the past 3 years (Number of adverse events/Total number supplied by year)	Year	No of similar AEs	Total number supplied	Frequency of occurrence (%)

Frequency of Occurrence of Similar Adverse Events in Singapore in the past 3 years (Number of adverse events/Total number supplied by year)	Year	No of similar AEs	Total number supplied	Frequency of occurrence (%)
No. of Patients Involved in this AE				
No. of Devices Involved in this AE				
Was the device implanted?	☐ Yes ☐ No Implantation Date:			
V – RESULTS OF PRODUCT OWNER'S INVESTIGATION				
Product Owner's Device Analysis results				
Device History Review				
Course of Action/ Remedial/ Corrective/ Preventive action				
VI – PATIENT INFORMATION (Please do not include patient name or any other patient identifiable information in this section)				
Age of patient at time of event *(years)*				
Gender				
Patient Outcome	☐ Recovered (Date *(dd/mm/yyyy)*:) ☐ Not yet recovered ☐ Death (Date *(dd/mm/yyyy)*:) ☐ Others (Please specify:)			
VII – HEALTHCARE FACILITY INFORMATION				
Name				
Address				
Contact Name at site of event				
Job title				
Tel no.				
Email Address				
VIII – OTHER INFORMATION				

☐ I attest that the information submitted is true and accurate, and that I am authorized to submit this form on behalf of the company.

Directorate General of Drug Administration
Mohakhali, Dhaka-1212.

Health Services Division
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

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