Pharmacovigilance Guidance Document

for

Marketing Authorization Holders of Pharmaceutical Products

सत्यमेव जयते

Published by

Indian Pharmacopoeia Commission
National Coordination Centre - Pharmacovigilance Programme of India
in Collaboration with Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India

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DISCLAIMER

The Pharmacovigilance Guidelines for Marketing Authorization Holders of pharmaceutical products in India is a regulatory guidance document. These guidelines are for the guidance of all stakeholders and are not meant to substitute or rephrase the rules made under Drugs and Cosmetics Act, 1940 and Rules 1945 or any other relevant act and are subject to being the conformity with the Drugs and Cosmetics Act, 1940 and Rules 1945 as may be amended from time to time. This document is meant to enable MAHs to set up a Pharmacovigilance system at their organization as per the recent amendment in Drugs & Cosmetics Act, 1940 and Rules, 1945. This document ensures the post-marketing surveillance of new and subsequently approved drugs, preparation & submission of Periodic Safety Update Reports, Quality Management System at MAH's organization, Audit & Inspection of Pharmacovigilance System at MAH's organization across the country under the purview of the competent authority. In the event of any dispute as regard to the content of this document and the statutes, the statutory provisions shall prevail. In case, there is an anomaly between the content of this document and any other non-statutory/official document, the decision of the Government of India or the implementing authority shall prevail.

PREFACE

The Pharmacovigilance Guidance document for Marketing Authorization Holders (MAHs) of Pharmaceutical Products in India is in consonance with the objective of Drugs and Cosmetics Act, 1940 and Rules there under and other functions of Central Drugs Standard Control Organization (CDSCO) wherever applicable. This guidance document is prepared under the aegis of CDSCO by National Coordination Centre (NCC) - Pharmacovigilance Programme of India (PvPI), the Indian Pharmacopoeia Commission (IPC) for guiding MAHs involved in the manufacture, sale, import and distribution of pharmaceutical products in India. The procedure set out to facilitate the pharmaceutical industry to submit the documents as per the requirements of Drugs and Cosmetics Act and Rules.

The guidance document defines the roles and responsibilities of CDSCO, IPC, NCC-PvPI, State(s)/UT(s) Drugs Regulatory Authority and MAHs in Individual Case Safety Reports (ICSRs) processing; submissions of Periodic Safety Update Reports (PSURs); Audits and Inspections and Risk Management Plan (RMP) wherever applicable. This guidance document also provides assistance to MAHs on establishing and ensuring an effective Pharmacovigilance system at their site. Guidance document may be amended from time to time after obtaining necessary approvals from the concerned authorities.

CONTENTS

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AIIMS	All India Institute of Medical Sciences
AMC	Adverse Drug Reaction Monitoring Centre
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDSCO	Central Drugs Standard Control Organization
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
CT	Clinical Trial
DCG (I)	Drugs Controller General (India)
DHPC	Direct Healthcare Professional Communication
E2B	Electronic Transmission of Individual Case Safety Report
FDA	Food and Drugs Administration
GoI	Government of India
HCP	Healthcare Professional
HQ	Head Quarter
ICD	International Classification of Diseases
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IPC	Indian Pharmacopoeia Commission
MAHs	Marketing Authorization Holders
MoHFW	Ministry of Health & Family Welfare
NCC	National Coordination Centre
PBRER	Periodic Benefit-Risk Evaluation Report
PIL	Patient Information Leaflet
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT	Preferred Term
PvPI	Pharmacovigilance Programme of India
Pv	Pharmacovigilance

PvMF	Pharmacovigilance System Master File
PvOI	Pharmacovigilance Officer In-charge
QMS	Quality Management System
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SJS	Stevens Johnson Syndrome
SOC	System Organ Class
SOP	Standard Operating Procedure
SmPCs	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UMC	Uppsala Monitoring Centre
UT	Union Teritory
WHO	World Health Organization
XML	Extensible Markup Language

A. INTRODUCTION

India is a hub of generic producer of medicines. In recent years, it has attained the status of "Pharmacy of the World". It supplies medicines to more than 200 countries and vaccines to 160 countries. India is a vast socio-ethnic, biodiverse country with different healthcare facilities for its myriad masses. Due to its varied geographical expanse, disease patterns and different practising systems of medicine, Indian population encounters Adverse Drug Reactions (ADRs) which is a phenomenon entirely different from other countries. Therefore, ADR monitoring with a broad-based scientific system in place will impact health indices of Indian population.

This guidance document focuses on Pv activities on a pharmaceutical product circulating in the market after post licensure period. This guidance document uses the term Pv as defined by WHO 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'. For the purpose of this guidance document, Marketing Authorization Holder (MAH) refers to the manufacturer or the importer of the drug, who has valid manufacturing or import license.

With every licensed pharmaceutical product there are benefits and risks associated. In order to obtain approval for human use, every licensed product should have benefits that outweigh the risks. The knowledge related to the safety profile of the product can change over time through expanded use in terms of subject characteristics and the number of patients exposed. In particular, during the early post marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on benefits and risks associated with the product; evaluation of this information should be a continuing process, in consultation with regulatory authority. Detailed evaluation of the information generated through Pv activities is important for all products to ensure their safe use.

This document rationally place guidance that all MAHs of pharmaceutical product (importers and manufacturers)should establish an appropriate Pv system with adequate number of qualified, trained, experienced manpower to collect, collate all AEs/ADRs. This Pv system at MAH organization should perform causality assessment of the collated AEs/ADRs cases mandatorily for new drugs whereas for subsequently approved drugs the MAHs are encouraged to perform the causality assessment and submit to regulatory authority/NCC-PvPI, IPC. In a comprehensive PSUR, all such information shall have to be placed as per the norms stipulated in Schedule-Y of Drugs & Cosmetics Act, 1940 and Rules 1945 and submitted to the licensing authority/NCC-PvPI in a timely manner.

A.1 Objective

This document intends to be an aid to the MAH's and other allied stakeholders who play an active role in launching, distribution and bringing the pharmaceutical products to its end users. The main focus of this guideline is to identify the risks associated with pharmaceutical products and establish a Pv system at MAH's organization to mitigate such risks.

A. 2 Scope

This document includes following category of pharmaceutical products:

- New Drugs, subsequently approved drugs.

- Biologics (Refer "Guidance for Industry on Pv Requirements for Biological Products" by CDSCO for vaccines along with this guidance documents)
- Radiopharmaceuticals
- Phytopharmaceutical products

This guidance document excludes veterinary products and medical devices.

B. ROLES AND RESPONSIBILITIES OF AUTHORITIES

B.1 Central Drugs Standard Control Organization

The Central Drugs Standard Control Organization (CDSCO) under Directorate General of Health Services in Ministry of Health and Family Welfare (MoHFW), Government of India (GoI) is the National Regulatory Authority (NRA) responsible for approval of new drugs, conduct of clinical trials, laying down the standards for drugs, control over the quality of imported drugs in the country and coordination of the activities of State Drugs Control Organizations by providing expert advice with a view to bring the uniformity in the enforcement and implementation of the Drugs and Cosmetics Act and Rules. As National Regulatory Authority, CDSCO has the responsibility to conduct the Pharmacovigilance Programme of India (PvPI). For the said purpose, National Coordination Centre (NCC) at IPC has been established to conduct pharmacovigilance under Pharmacovigilance Programme of India. Various ADR monitoring centres have been established in various medical colleges across the country, which are reporting to PvPI at IPC through VigiFlow software.

As a condition of the marketing authorization, the MAH is also required to submit PMS/PSUR after licensure of the pharmaceutical product. The PSURs are to be submitted every six months for first two years of the approval and for subsequent two years annually. The Licensing Authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. The compiled PSUR data should then be reviewed by CDSCO in consultation with expert committee. Based on the analysis of the expert committee regulatory decision should be taken by CDSCO on safety and efficacy of the pharmaceutical products. The data emerging beyond the initial post licensure studies through PSUR or any other PMS studies shall form the basis of further decisions about indications/usage/restrictions on indications of the pharmaceutical product and further decision on extension of duration of submission of PSUR data beyond 4 years may be taken by Licensing Authority.

CDSCO is also responsible to take appropriate regulatory decision on the basis of recommendations of Signal Review Panel (SRP) of NCC-PvPI at IPC to assess the database for the occurrence of signals of possible importance for public health, drug regulation, and science. CDSCO is responsible to take regulatory decision on the basis of analysis of the PSUR data. Evidence-based information should be utilized for appropriate regulatory decision by the CDSCO such as changing/updating package-insert, issuing drug alerts, and signals, if any.

B.1.1 State Drug Control Authority:

Drugs fall under the Concurrent List of the Constitution of India. Drugs & Cosmetics Act is a Central Act enforced by both Central and State Governments. Every State and Union Territory of India has its own Drugs Regulatory Authorities. State Drugs Controllers are primarily responsible for licensing of manufacturing and sale/distributionof drugs.

As per the requirements under sub para(2) of Para 28 of Schedule M (Good manufacturing practices and

requirements of premises, plant and equipment for pharmaceutical products) of Drugs and Cosmetics Act and Rules, "Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority." Therefore, it is required under Rule to monitor Adverse Drug Reactions/ complaints related to drugs marketed in the country by the MAH & submit to the licensing authority/NCC-PvPI, IPC.

B.2 Pharmacovigilance Programme of India (PvPI) at Indian Pharmacopoeia Commission (IPC)

A robust techno-science-based system in the form of PvPI was launched in 2010, initially housed at AIIMS, New Delhi, as a National Coordination Centre (NCC). As many as 22 AMCs were functioning under AIIMS of which 40% were functional. The MoHFW decided to recognize the Indian Pharmacopoeia Commission (IPC), an autonomous institute under the aegis of MoHFW, GoI in 2011 as a NCC for PvPI. IPC was created to set standards of drugs in the country. Its basic function is to update regularly the standards of drugs commonly required for treatment of diseases prevailing in this region. It publishes official documents for improving quality of medicines by way of adding new and updating existing monographs in the form of Indian Pharmacopoeia (IP). It further promotes rational use of medicines by publishing National Formulary of India (NFI).

The IPC as a NCC for PvPI has been striving hard in collaboration with national and international stakeholders, ensuring patients' safety by monitoring ADRs. Realizing the importance of Pv in recent years, the IPC has established a nationwide network with different genre of healthcare professionals and the outreach of PvPI to 250 AMCs. India specific ADRs generated in 2010 were 9,000 while the current ADRs reported under the umbrella of PvPI is as enormous as 260,000. The NCC-PvPI, IPC also participates in the international drug-monitoring programme by contributing ADRs to UMC, a WHO-collaboration centre. India is one of the significant contributors to WHO in terms of quantity and quality of ADRs reporting.

The PvPI has succeeded in establishing AMCs across the country, upgrading capacity- building and training to the stakeholders, besides encouraging hospitals, individuals and civil society to participate in PvPI. Several tools and methods have been introduced by the PvPI to report ADR in Hindi, English and other vernacular languages, mobile apps, helpline - 18001803024 (toll-free), etc. PvPI has also been working hand in hand with other Public Health Programmes (NHPs) such as Revised National Tuberculosis Control Programme (RNTCP), National Aids Control Programme (NACO) and National Vector-Borne Disease Control Programme (NVBDCP).

PvPI Signal Review Panel consists of national, experienced medical professors, regulatory authority members usually affiliated to a government or academic institution invited by NCC-IPC. Under the responsibility of PvPI, they assess the database for the occurrence of signals of possible importance for public health, drug regulation, and science.

This stable system has enabled PvPI to collect, collate and analyze data scientifically which should be utilized for appropriate regulatory decision by the CDSCO.

B.2.1 PvPI - Programme Communication

Effective communication channels are key to successful functioning of PvPI. Using the latest Information Technology tools for effective communication across its 250 ADR monitoring centres, NCC-PvPI ensures continuous transfer of data and information across the public healthcare spectrum as given in Figure-1.

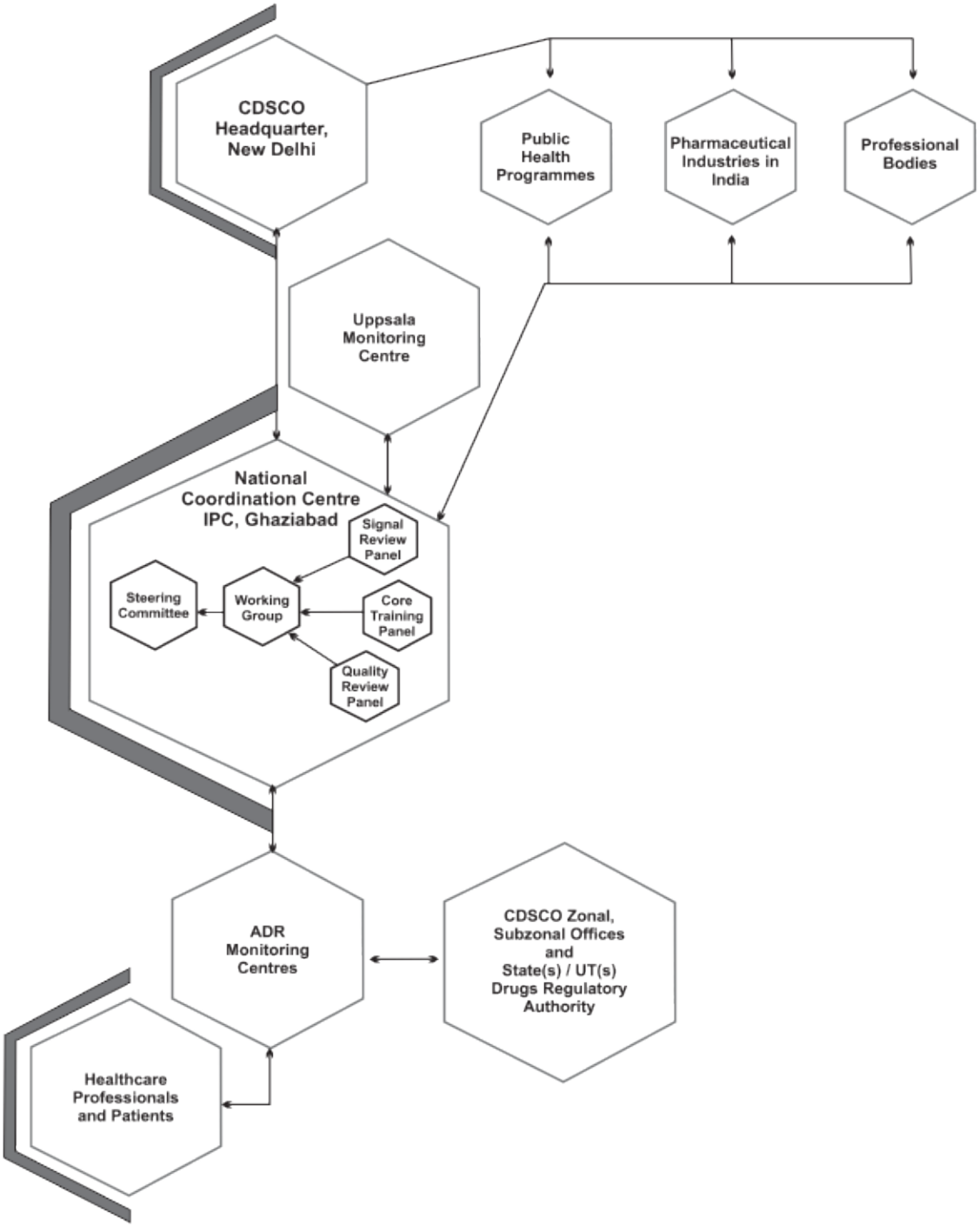

Figure 1: PvPI-Programme Communication

C. MODULES

Module 1	-	Pharmacovigilance System Master File
Module 2	-	Collection, Processing & Reporting of Individual Case Safety Report
Module 3	-	Preparation & Submission of Periodic Safety Update Report
Module 4	-	Quality Management System at MAH's organization
Module 5	-	Audits and Inspections of Pharmacovigilance systems at MAH's organization
Module 6	-	Submission of Risk Management Plan

MODULE 1

Pharmacovigilance System Master File

Contents:

1.1 Introduction

This module provides detailed guidance regarding the requirements for the PvMF, including its maintenance, content and associated submissions to competent authorities. The PvMF file shall be located at the MAH's organization in India where the main Pv activities of MAHs are performed. MAHs are required to collect and process comprehensive safety information related to pharmaceutical products and report to regulatory authority within the prescribed timelines. Every MAH shall have a system in place that ensures overall quality of AEs/ADRs.

1.2 Scope

This guidance document encompasses requirements for the PvMF for pharmaceutical products authorized in India, irrespective of the marketing authorization procedure followed by the licensing authorities.

1.3 Objective

- Obtain information about deficiencies in the system, or non-compliance with the requirements;
- Obtain information about risks or actual failure in the conduct of specific aspects of Pv.

1.4 Contents of the PvMF

The PvMF shall contain all the information related to MAH's Pv system and shall cover the following sections:

1.4.1 Pharmacovigilance Officer In-charge

In compliance with Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules,1945, one qualified and trained personnel should be authorized by the company management as PvOI with responsibilities for dealing Pv activities at MAH's organization. This PvOI should be a medical officer or a pharmacist trained in the collection and analysis of ADR reports. PvOI shall be responsible for the following:

- Development of training modules and organizing training for staff of Pv department;
- Identification of Pv activities and framing of SOPs, revision of SOPs;
- Establishment and maintenance of QMS of Pv department;
- The PvOI should reside in India and respond to queries of regulatory authorities whenever required. The information relating to the PvOI provided in the PvMF shall include:
    - Contact details (Name, address, phone, e-mail);
    - Summary, curriculum vitae with the key information on the role of the PvOI;
    - A description of the responsibilities guaranteeing that the PvOI has sufficient authority over the Pv system in order to promote, maintain and improve compliance;
    - Details of duty-in-charge to work in the absence of PvOI;

1.4.2 Pharmacovigilance organization structure

1.4.2.1 MAH

Description of MAHs Pv hierarchy must be provided. The description should provide a clear overview of the company(ies) and their allied Pv departments involved and the relationship(s) between organizations and operational units relevant to the fulfillment of Pv obligations.

1.4.2.2 Contract Research Organization

If MAH assigns the responsibilities of Pv activities of their pharmaceutical products to any CRO, then a clear overview of the company(ies) and their allied Pv departments involved and the relationship(s) between organizations and operational units relevant to the fulfilment of Pv obligations should be provided. It should include:

- The Pv organizational structure of the MAHs/CRO's showing the hierarchy of the Pv department in the organization;
- Name & address of the organization where the Pv functions are undertaken covering ICSRs processing, preparation & submission of PSURs, signal detection, RMP, post-marketing surveillance and management of safety variations;
- Delegated activities (contracts and agreements);
- Service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.);
- Commercial arrangements (distributors, licensing partners, co-marketing etc.);
- Technical providers (hosting of computer systems etc.)

1.4.3 Sources of safety data

The PvOI shall be responsible to collect data, reports, publications related to safety of all pharmaceutical products marketed by the MAH. The main source for safety data shall be as follows:

- Medical information inquiries;
- “Contact us”emails, website inquiry forms and help-line;
- Pharmaceutical Product market complaints;
- MAH employees involved in Pv activities;
- Spontaneous information from patient;
- Published literatures;
- Spontaneous reporting by consumers/HCPs;
- Reports from internet or digital media or social media;
- Patient-support programmes;

- Reports from regulatory authority;
- Contract partners involved in Pv activities;

1.4.4 Pharmacovigilance Processes

1.4.4.1 Description

A description and flow-diagram of the entire Pv process, data handling, records and archives of Pv performance, covering the following aspects shall be included in the PvMF:

- ICSR collection, collation, processing, assessment, reporting and follow-up; the procedures applied to this area should clarify the activities;
- Compilation of all ICSR and preparation & submission of PSURs of new drugs in accordance with Schedule Y of Drugs & Cosmetics Act, 1940, Rules 1945;
- Review of ICSR, detection of signal (if any), CAPA;
- Communication of safety concerns to consumers, HCPs and the competent regulatory authorities;
- SmPCs and PILs , with history of revisions

1.4.4.2 SOP should include the following:

- Description of the process, data handling and records of Pv performance;
- ICSR collection, collation, follow-up, assessment and reporting;
- PSUR scheduling, preparation and submission;
- Quality issue, recall or withdrawal of pharmaceutical products;
- Training procedures and documentations;
- Signal detection and evaluation process;
- Communication of safety concerns to consumers, HCPs and regulatory authorities;
- Implementation of safety variations in PILs/SmPCs;
- Safety data exchange agreements, if any;
- Safety data archival and retrieval;
- Pv audit & inspection readiness;
- Quality Control for Pv activities;

1.4.4.3 Computerized systems and database

The location, functionality and operational responsibility for computerized systems and databases for receiving, collating and reporting safety information should be described in PvMF. Validation status of computer system functionality with change control, if any; nature of testing; back-up procedures should also be described. The MAH can have data collection in Excel spreadsheets to record and track data.

1.4.4.4 QMS in Pharmacovigilance

A QMS should be established in Pv activities, which should include:

- **Document and record control:** The MAHs should retain the soft copy back-up of all Pv documents for indefinite time and hard copies for at least 10 years. The MAHs shall maintain a logbook for recording primary information received for every AEs/ADRs reported.
- **Training:** A summary description of the training concept, including a reference to the location of the training files. Staff should be appropriately trained for performing Pv-related activities, including any individual who may receive safety reports.
- **Auditing:** The QA of the company should supervise the internal & external audits of Pv system. The audit report must be documented within the quality system; with a brief description of the CAPA associated with the significant finding, the date it was identified and the anticipated resolution date(s) with cross reference to the audit report and the documented CAPA plan(s).

1.4.5 Pharmacovigilance system performance

The key indicators for the performance of Pv system e.g. number and quality of ICSRs, CAPA needs to be identified and measured for annual trend analysis.

PvMF should contain evidence of the ongoing monitoring of the Pv system performance, including compliance of the main Pv output. The PvMF should include a description of the monitoring methods applied and contain as a minimum:

- An explanation of how the correct reporting of ICSRs is assessed. In the annexure, figures/graphs should be provided to show the timelines of submission;
- A description of any metrics used to monitor the quality of submissions and performance of Pv. This should include information provided by the regulatory authority regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timelines of PSUR reporting;
- An overview of the methods used to ensure the timelines of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet submitted;
- Wherever applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to Pv.

1.5 Annexures to the PvMF

- A list of pharmaceutical products covered by the PvMF, including the name of the pharmaceutical product and active substance(s);
- A list of contract agreements covering delegated activities, including the pharmaceutical products and territory(ies) concerned;
- A list of tasks delegated by the PvOI for Pv;
- A list of all completed audits (regulatory as well as internal), and a list of audit schedules.

MODULE 2

Collection, Processing & Reporting of Individual Case Safety Reports

Contents:

2.1 Introduction

This section highlights the general principles in relation to the collection, processing and reporting of all AEs/ADRs associated with pharmaceutical products for human use, which are applicable to MAHs.

2.2 Structure & Processes

2.2.1 Collection of ICSR

Under-reporting of AEs/ADRs is a well-known problem associated with spontaneous reporting, therefore, MAHs shall have different sources/methods to report AEs/ADRs to the organization. The following sources/methods required to be established by MAHs to strengthen spontaneous reporting.

2.2.1.1 Medical inquiries

MAHs shall have a process in place to record all the medical inquiries related to their pharmaceutical products and document due diligence made in seeking follow-up information or clarifications with a patient/consumer or HCP. For inquiries that relate to safety of the pharmaceutical product, MAHs should ensure there is a mechanism in place to transfer details of such cases to the Pv point of contact. Reconciliation activities between the appropriate/corresponding departments should also be undertaken periodically.

2.2.1.2 "Contact us", e-mails and website inquiry forms

The MAH must consider the mechanism by which incoming information via "Contact us" pages through e-mail addresses or website inquiry forms is monitored to allow the identification and transfer of Pv data to the designated Pv person in an appropriate time frame to meet regulatory requirement.

2.2.1.3 MAH's employees

The employees of the MAH designated for the Pv work, should be trained timely on the type of information and data collection being received from various sources. These employees should be well versed in dealing with the information i.e. how to report particular AEs/ADRs. The data captured manually by the medical representative during a discussion with a HCP regarding an AE or other safety related issue should be retained and he/she should be aware of reporting the same to the Pv personnel of the respected MAHs.

2.2.1.4 Contractual partners

There are different types of contractual partnership existing in the pharmaceutical industry, like loan licensing, contract manufacturing, distribution etc. The responsibilities regarding Pv activities among partners shall be clearly defined in a safety data exchange agreements. Contractual partners are a potential source of ICSR and mechanisms should be in place for the exchange of these ICSR in an appropriate timeframe to meet regulatory requirements.

2.2.1.5 Information on AEs/ADRs from the internet or digital media

MAHs should regularly screen relevant website or digital media (including newspapers) or social media under their management or responsibility, for potential reports of AEs/ADRs. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the MAHs. The frequency of the screening should allow for potential valid ICSR to be reported to the competent authorities within the

appropriate reporting timeframe based on the date the information was posted on the website/digital media. MAHs may also consider utilising their websites to facilitate the collection of AEs/ADRs.

2.2.1.6 Solicited reports

As defined in ICH-E2D, solicited reports of suspected ADRs are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected ADRs obtained from any of these data collection systems should not be considered spontaneous.

2.2.1.7 Miscellaneous sources for reporting

The MAH should have other methods like e-mail, fax, online submission, mobile app, helpline, postal letters etc. to report AEs/ADRs. Patient identity should be kept confidential.

2.3 Literature monitoring

The scientific and medical literature is a significant source of information for monitoring of the safety and benefit-risk profile of pharmaceutical products, particularly in relation to the detection of new safety signals or emerging safety issues. MAHs shall perform monthly literature review of their pharmaceutical products by using electronic literature data base (such as Pubmed etc.). Any AE/ADR identified by this process need to be processed as per spontaneous ICSR.

2.4 Follow-up ICSR

When initial ICSR is received, the information on AEs/ADRs may be incomplete. Such ICSR should be followed-up as necessary to obtain supplementary detailed information (Refer section 2.6.1, Essential data element of ICSR) required for clinical evaluation of the ICSR. Any attempt to obtain follow-up information should be documented and any new significant information must be reported to NCC-PvPI, IPC. This should be highlighted in the case narrative of the ICSR.

2.5 Processing of ICSR

2.5.1 ICSR receipt

2.5.1.1 Date of receipt

MAH shall record the date of receipt for each AEs/ADRs; this applies to both initial notification and any follow-up communication.

2.5.1.2 Validation of reports

All reports of AEs/ADRs shall be validated before reporting them to the NCC-PvPI, IPC. In order to ensure the minimum criteria for reporting, the following essential elements required to be provided:

- An identifiable reporter (source);
- An identifiable patient;

- A suspect pharmaceutical product;
- An AE/ADR.

When all the above essential elements are reported in an individual report, it is then referred as an ICSR.

2.6 Reporting of ICSR

All ICSRs received by MAHs shall be submitted to NCC-PvPI, IPC in E2B, xml format (Refer Appendix-A).

2.6.1 Essential data elements of ICSR

Each ICSR should contain the following mandatory fields:

2.6.1.1 Patient information

- ***Patient initials*:** Write first letter of name & surname e.g. Vipin Sharma should be written as VS.
- ***Age at the time of onset of event or date of birth:*** Write either the date of birth (DD/MM/YYYY) or age of the patient at the time of an event or reaction occurred.
- ***Sex:*** Mention the gender of the patient e.g. male, female, others (transgender)
- ***Weight**:* Mention the weight (kg) of the patient.

2.6.1.2 Suspected reaction

- ***Date of reaction started:*** Mention the date on which the reaction was first observed.
- ***Date of reaction stopped:*** If the reaction recovered, the date on which the patient recovered from the reaction should be reported.
- ***Describe reaction:*** Provide the description of the reaction in terms of nature, localization, etc. e.g patient developed erythematous maculopapular rash over upper and lower limb.

2.6.1.3 Suspected medication(s)

1. The details of suspected medication(s) such as drug name (brand or generic name), manufacturer batch no/lot no., expiry date, authorization holder, dose, route, frequency, dates of therapy started and stopped, and indication should be provided by the reporter.
2. ***De-challenge details:*** Mention the status on de-challenge as-

- **'Yes'**-If the reaction abate after de-challenge
- **'No'**- If the reaction did not abate after de-challenge
- **'Unknown'-** If an effect of de-challenge is not known

3. ***Action Taken:*** Mention the status of action taken at the time of AE/ADR reporting as-

- Drug withdrawn

- Dose reduced
- Dose increased
- Dose not changed
- Unknown
- Not Applicable

4. ***Re-challenge details:*** Mention the status on re-challenge as-

- **'Yes'**-If the reaction reappeared after re-challenge
- **'No'**- If the reaction did not reappear after re-challenge
- **'Effect unknown'-** If an effect of re-challenge is not known

5. ***Concomitant drugs:*** Write the details of all concomitant drugs, including self-medication, Over The Counter medication, herbal remedies, etc. with therapy dates.

6. ***Relevant tests/ laboratory data:*** Mention relevant laboratory tests/data before & after AEs/ADRs

7. ***Other relevant history:*** Write the relevant history pertinent to patient, including pre-existing medical conditions (e.g. allergies, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction) and concurrent condition, if any.

8. ***Seriousness of the reaction****:* If any reaction is serious in nature, tick the appropriate reason for seriousness as-

- **Death:** If the patient died, mention the cause of death and date in the seriousness of the reaction.
- **Life-threatening:** If the patient was at substantial risk of dying at the time of AEs/ADRs.
- **Hospitalisation/prolonged:** if AEs/ADRs caused hospitalization or increased the hospital stay of the patient.
- **Disabling:** If AEs/ADRs resulted in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly**: If exposure of the drug prior to conception or during pregnancy may have resulted in a birth defect in the child.
- **Other medically important condition:** When the event does not fit above conditions, but the event may put the patient at risk and may require medical or surgical intervention to prevent one of the above conditions. Examples include serious blood disorders or seizures/convulsions that do not result in hospitalization, development of drug dependence or drug abuse.

9. ***Outcomes:*** Tick the outcome of the event at the time of AE/ADR reporting as-

- **Recovered/resolved:** If the patient recovered/resolved from the reaction

- **Not recovered/not resolved:** If the patient did not recover/resolv from the reaction
- **Recovering/resolving:** If the patient is recovering/resolving from the reaction
- **Fatal-** If the patient died
- **Recovered/resolved with sequelae**- If the patient has completely recovered from the reaction (mention the date of recovery) or recovered with sequelae (e.g scar).
- **Unknown-** If the outcome is not known

2.6.1.4 Reporter

- ***Name & professional address:*** A reporter must mention his/her name, professional address and contact details. The identity of the reporter will be maintained confidential.
- ***Date of report:*** Mention the date on which he/she reported the AEs/ADRs.
- ***Reporter qualification*:** Qualification of the reporter need to be mentioned.

2.7 Coding

For the purpose of ICSR reporting (expedited and periodic) to regulatory authority/NCC-PvPI, IPC MAHs are required to code ADRs using the ADRs' coding dictionary and indication of suspected and concomitant drugs using the latest version of ICD. Coding of reports also facilitates the process of signal detection and benefit-risk assessment.

2.8 Reporting time frames

- All serious unexpected Adverse Reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant.
- All serious AEs/ADRs must be reported to the regulatory authority/NCC-PvPI, IPC within 15 days of initial receipt of the information by the MAHs.
- All non-serious AEs/ADRs must be reported to the NCC-PvPI, IPC within 30 days of initial receipt of the information by the MAHs.

Note : *Lack of efficacy, medication error etc. must also be reported to regulatory authority/NCC-PvPI, IPC.*

2.9 Causality assessment

The MAHs should preferably follow WHO-UMC causality assessment scale for establishing a causal relationship between the suspected drugs and AEs. The WHO-UMC scale is used as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

For WHO-UMC causality assessment scale, refer Appendix -B.

Note: *The causality assessment for new drugs is mandatory by the MAHs*

2.10 Special population

2.10.1 Use of a pharmaceutical product during pregnancy or breastfeeding

Reports, where the embryo or foetus may have been exposed to pharmaceutical products should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the pharmaceutical product was taken before conception.

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

Individual cases with an abnormal outcome associated with a pharmaceutical product following exposure during pregnancy are classified as serious reports and should be reported, especially:

- Reports of congenital anomalies or developmental delay, in the foetus or the child;
- Reports of foetal death and spontaneous abortion;
- Reports of suspected adverse reactions in the neonate that are classified as serious.

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be reported. This may be a condition of the marketing authorisation or stipulated in the risk management plan; for example pregnancy exposure to pharmaceutical products contraindicated in pregnancy or pharmaceutical products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin). A signal of a possible teratogenic effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the regulatory authority.

Note : *ADRs which occur in infants following exposure to a pharmaceutical product from breast milk should be reported.*

2.10.2 Use of a pharmaceutical product in a paediatric or elderly population

The collection of safety information in the paediatric 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 case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population.

MODULE 3

Preparation & Submission of Periodic Safety Update Report

Content:

3.1 Introduction

3.2 Objective

3.3 General principles

3.4 Structure & content

3.1 Introduction

The Periodic Safety Update Report is a document for evaluation of the benefit-risk profile of a pharmaceutical product submitted by the MAH at defined time points as per Drugs and Cosmetics Act, 1940 and Rules thereunder during the post-marketing phase.

3.2 Objective

This guidance document defines the recommended format, content and timeline of PSUR submission in conformity with Schedule 'Y' of the Drugs and Cosmetics Act, 1940 and Rules, 1945. PSURs are intended to be submitted to regulatory authorities and NCC-PvPI, IPC by the MAHs during the post-marketing phase, in order to monitor the safety and efficacy of pharmaceutical products marketed in India.

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of new or emerging information on the risks and benefits of the pharmaceutical products in approved indications. The PSUR, is therefore, a tool for post-marketing evaluation at defined time points in the life cycle of a pharmaceutical product.

3.3 General principles

As per "Schedule Y" of Drugs and Cosmetics Act, 1940 and Rules, 1945 point (4) Post Marketing Surveillance-

(i) Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish PSURs in order to-

(a) Report all the relevant new information from appropriate sources;

(b) Relate these data to patient exposure;

(c) Summarize the market authorization status in different countries and any significant variations related to safety;

(d) Indicate whether changes should be made to product information document in order to optimize the use of the pharmaceutical product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate presentations of data for different dosage forms, indications or separate population needs to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The PSURs shall be submitted every six months for the first two years after approval of the drug is to the applicant. For the subsequent two years - the PSUR need to be submitted annually. The licensing authority may extend the total duration for submission of PSUR if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious AEs/ADRs must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to the market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the PSUR.

3.4 Structure & content

The recommended content of the PSUR should have data as per Schedule Y of Drugs and Cosmetics Act, 1940 and Rules 1945, Section (4) Post-Marketing Surveillance (PMS) and ICH-E2C (R2) guideline. The structure and content of PSUR is appended below :

1. Title Page
2. Introduction
3. Current worldwide marketing authorization status
4. Update of actions taken for safety reasons
5. Changes to Reference Safety Information like PIL, CCDS & SmPCs
6. Estimated patient exposure
    - 6.1 Cumulative subject exposure in clinical trials
    - 6.2 Cumulative and interval patient exposure from marketing experience in India
    - 6.3 Cumulative and interval patient exposure from marketing experience from rest of the world
7. Presentation of individual case histories
    - 7.1 Line listing of individual cases received from India
    - 7.2 Line listing of individual cases received from rest of the World
    - 7.3 Cumulative summary tabulations of SAEs from clinical trials
    - 7.4 Cumulative and interval summary tabulations from Post-Marketing data sources
8. Studies
    - 8.1 Summaries of significant findings from clinical trials during the reporting period
    - 8.2 Findings from non-interventional studies
    - 8.3 Information from other clinical trial sources
    - 8.4 Findings from non-clinical studies
    - 8.5 Findings from literature
9. Other Information
    - 9.1 Lack of efficacy in controlled clinical trials
    - 9.2 Late-Breaking Information

9.3 Overview of Signals: New, Ongoing, or Closed

10. Overall Safety Evaluation

10.1 Signal and Risk Evaluation

10.2 Benefit Evaluation

10.3 Benefit-Risk Analysis Evaluation

11. Conclusions

12. Appendix to the PSUR

1. Title Page

The title page of the PSUR should include the following information:

- Date of reporting
- Name of the Pharmaceutical product(s) including both Inter National Non Proprietary Name (INN) and Brand Name
- Period covered by the report
- Approved indication of pharmaceutical products
- Date of approval of the drug
- Date of marketing of the drug
- Address of MAH
- Any statement on the confidentiality of the information included in the PSUR.

2. Introduction

A brief introduction of product(s) so that the PSUR "stands alone" but it is also placed in perspective relative to previous PSURs and circumstances shall be given by MAHs. The introduction should contain the following information:

- Reporting interval
- Pharmaceutical product(s) - mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s)
- A brief description of the approved indication(s) and population(s)
- A brief description and explanation of any information that has not been included in the PSUR
- The rationale for submission of multiple PSURs for the pharmaceutical product, if applicable

3. Current worldwide marketing authorization status

This section of PSUR should capture the brief narrative overview, including details of the country where the pharmaceutical product is currently approved along with date and country of first approval, date of marketing and, if the pharmaceutical product was withdrawn in any of the countries with reason thereof. The information related to current worldwide marketing authorization status can be provided as an Annexure to the PSUR.

4. Update of actions taken for safety reasons

This section of PSUR should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- A significant influence on the benefit-risk profile of the approved pharmaceutical product;
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.
- If known, the reason(s) for each action should be provided, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarized in this section e.g. history of the following before approval:
- Refusal to authorize a clinical trial for ethical or safety reasons for the marketed molecule before obtaining licensing;
- Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- Recall of investigational drug or comparator;
- Failure to obtain marketing approval for a tested indication, including the voluntary withdrawal of a marketing application;
- Risk management activities
    - ✓ History of protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in clinical trial duration)
    - ✓ History of partial suspension might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses).
    - ✓ Restrictions in study population or indications;
    - ✓ Changes to the Informed consent document relating to safety concerns;
    - ✓ Formulation changes;

- ✓ Addition by regulators of a special safety-related reporting requirement;
- ✓ Issuance of a communication to investigators or HCPs;
- ✓ Plans for new studies to address safety concerns.

Actions related to drugs after approval

- Failure to obtain or apply for a marketing approval renewal
- Withdrawal or suspension of a marketing approval
- Suspension of supply by the MAH
- Risk management activities:
  - ✓ Significant restrictions on distribution or introduction of other risk minimization measures,
  - ✓ Significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated,
  - ✓ Communications to HCPs
  - ✓ New post-marketing study requirement(s) imposed by the regulator(s).

5. Changes to Reference Safety Information

This PSUR section should list any significant changes made to the RSI like PIL & CCDS/SmPC within the reporting interval. MAH should also specify the date and country of approval of RSI in narrative.

Note: *In case there is no significant change in RSI (PIL & CCDS/SmPCs), MAHs should submit recent dated approved RSI as an Annexure.*

6. Estimated patient exposure

This section should provide estimates of the size and nature of the population exposed to the pharmaceutical product. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR introducing the change and any important difference between the results using the two methods should be highlighted.

6.1 Cumulative subject exposure in clinical trials

This section of the PSUR should include the following information in tabular format as referred below:

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational pharmaceutical product, placebo, and/or active comparator(s) since the date of first approval for conducting an interventional clinical trial in any country (Refer Appendix-C, Table 01).
- More detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-

grouped by age, sex, and racial/ethnic group) important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered (Refer Appendix-C, Table No. 02 & 03);

- If clinical trials have been or are being performed in special population (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate.
- When there are substantial differences in the time of exposure between subjects randomized to the investigational pharmaceutical product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years).
- New drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of ADR, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If the SAE from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately, if available.

6.2 Cumulative and interval patient exposure from marketing experience in India

Separate estimations should be provided for interval exposure (since the data lock points of the previous PSUR) and, when possible, cumulative exposure (since the date of marketing authorization) from India. (Refer Appendix-C, Table No. 04 and 05). The estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the same. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. If applicable, data of special population and vulnerable population should be identified and submitted.

The data should be presented according to the following categories:

6.2.1 Post-approval (non-clinical trial) exposure

An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by indication, sex, age, dose, formulation, and region, wherever applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. Whenever there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

6.2.2 Post-approval use in special population

Where post-approval use has occurred in special population, available information regarding cumulative patient numbers exposed and the method of calculation should be provided.

Sources of such data include non-interventional studies designed to obtain this information, including registries. Population to be considered for discussion include, but might not be limited to:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- Vulnerable population;
- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub-population carrying relevant genetic polymorphism(s);
- Patients of different racial and/or ethnic origin.

6.2.3 Other post-approval use

If the MAH becomes aware of patterns of use of the pharmaceutical product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g., an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). If known, the MAH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. If allowed by the law, the law suit case should also be included.

6.3 Cumulative and interval patient exposure from marketing experience from rest of the world

The estimations should be provided separately for interval exposure (since the data lock points of the previous PSUR) and, when possible, cumulative exposure from the date of approval in the rest of the world. (Refer Appendix-C, Table 06 and 07). The data should be presented as mentioned in the section 6.2.

7. Presentation of individual case histories

This section of PSUR should provide the individual case information potentially available to the MAH, provide brief case narrative with supportive investigational reports (wherever possible), concomitant medications, medical history, indication treated with suspect drug(s), de-challenge, re-challenge and causality assessment. The following information is required:

7.1 Line listing of individual cases received from India

The line listing of ICSRs should contain the following information: age, gender, seriousness criteria, ADR start/stop date, therapy start/stop date of suspected/concomitant drug, indication of suspected/concomitant drug, relevant past medical history, outcome & causality in tabulated form.

7.2 Line listing of individual cases received from rest of the world

The information required for line listing of ICSRs from rest of the world refer section 7.1.

7.3 Cumulative summary tabulations of serious adverse events from clinical trials

This section of the PSUR should provide background for the Appendix that provides a cumulative summary tabulation of SAE reported in the MAHs, clinical trials, from the first authorization to conduct a clinical trial in any country worldwide to the data lock point of the current PSUR. The MAHs should explain any omission of data (e.g., clinical trial data might not be available for pharmaceutical products marketed for many years). The tabulation(s) should be organized by SOC, for the new drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables.

This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix C, Table 08 provides summary tabulations of SAEs from clinical trials. The following points should be considered:

- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include non- serious events.
- While coding for the AE/ADR terms, the Preferred Term (PT) level and SOC should be presented in the summary tabulations.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors/manufacturers and/or importers should not unblind data for the specific purpose of preparing the PSUR.
- Certain AE in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, AEs that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

7.4 Cumulative and interval summary tabulations from Post-Marketing data sources

This section of the PSUR should provide background for the Appendix that provides cumulative and interval summary tabulations of ADRs, from the date of marketing authorization to the data lock point of the current PSUR. The tabulation should include:

- Serious and non-serious AEs/ADRs from spontaneous ICSR, including reports from HCPs, consumers, scientific literature, and regulatory authorities
- Serious adverse reactions from non-interventional studies
- Solicited reports of serious ADRs

For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented (Refer Appendix-c, Table 09).

8. Studies

8.1 Summaries of significant findings from clinical trials during the reporting period

This section of the PSUR should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the manufacturer and/or importer's sponsored clinical trials that became available during the reporting interval of the report. Whenever possible and relevant, data categorized by sex and age (particularly children versus adult), indication, dose, and region should be presented.

MAH -sponsored post-marketing interventional trials with the primary aim of identifying, characterizing, or quantifying a safety hazard, or confirming the safety profile of the pharmaceutical product that were completed or ongoing during the reporting interval should be included in an Appendix. The listing should include the following information for each trial:

- Study ID (e.g., protocol number or other identifier);
- Study title (abbreviated study title, if applicable);
- Study type (e.g., randomized clinical trial, cohort study, case-control study);
- Population studied (including country and other relevant population descriptors, e.g., paediatric population or trial subjects with impaired renal function);
- Study start (as defined by the manufacturer and/or importer) and projected completion dates;
- Status: Ongoing (clinical trial has begun) or Completed (clinical study report is finalised).

8.1.1 Completed clinical trials

This sub-section of the PSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in a narrative format or as a synopsis (Refer ICH-E3). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.2 Ongoing clinical trials

If the manufacturer and/or importer is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with Adverse Events), this sub-section should briefly summarize the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.3 Long-term follow-up

Wherever applicable, this sub-section should provide information from long-term follow-up of subjects

from clinical trials of new drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

8.1.4 Other therapeutic uses of pharmaceutical product

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the manufacturer and/or importer that follow a specific protocol (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient Investigational New Drug applications [INDs], treatment INDs, and other organized data collection).

8.1.5 New safety data related to fixed combination therapies

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the product that is the subject of a PSUR is also approved or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarize important safety findings from the use of the fixed dose combination therapy
- If this PSUR is for a fixed combination product, this section should summarize important safety information arising from the individual components
- The information specific to the combination can be incorporated into a separate section(s) of the PSUR for one or all of the individual components of the combination.

8.2 Findings from non-interventional studies

This section should summarize relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH -sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilization studies when applicable to multiple regions.

8.3 Information from other clinical trial sources

8.3.1 Other clinical trials

This sub-section should summarize information accessible with reasonable and appropriate effort from any other clinical trial/study sources to the MAH during the reporting interval (e.g. including results from pooled analyses or meta-analyses of randomized clinical trials, and safety information provided by co-development partners or from investigator-initiated trials).

8.3.2 Medication errors

This sub-section should summarize relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. This information may be received by the manufacturer and/or importer via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

8.4 Findings from non-clinical studies

This section should summarize major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval.

8.5 Findings from literature

This section should summarize new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved pharmaceutical product that the manufacturer and/or importer became aware of during the reporting interval.

Literature searches for PSUR should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

This should include:

- Pregnancy outcomes (including termination) with no adverse outcomes
- Use in paediatric populations
- Compassionate supply, named patient use
- Lack of efficacy
- Asymptomatic overdose, abuse or misuse
- Medication error where no adverse events occurred
- Important non-clinical safety results

9. Other Information

9.1 Lack of efficacy in controlled clinical trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for pharmaceutical products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular AEs in a trial of a new anti-platelet drug for Acute Coronary Syndromes) could reflect a significant risk to the treated population and should be summarized in this section.

9.2 Late-breaking information

This section should summarize information on potentially important safety and efficacy/effectiveness findings that arise after the data lock point but while the PSUR is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the manufacturer and/or importer, a data monitoring committee, or a regulatory authority has taken for the safety reasons.

Any significant change proposed to the reference product information which has occurred after the data lock point of the report, but before submission should also be included in this section, where feasible. Such

changes could include a new contraindication, warning/precaution, or new ADR.

9.3 Overview of signals: new, ongoing, or closed

A new signal is a signal that the MAH became aware of during the reporting interval. A new clinically important information on a previously closed signal that became available during the reporting period of the PSUR (i.e., a new aspect of a previously refuted signal or recognized risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR. Examples would include new information on a previously:

- Closed and refuted signal, which would result in the signal being re-opened;
- Identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g., transient liver enzyme increases are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well-documented and unconfined case report of agranulocytosis is received;
- Identified risk for which a higher frequency of the risk is newly found, e.g., in a sub population; and
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimization activities.

Refer Appendix-D, include a tabular listing of all signals ongoing or closed at the data lock points of the PSUR.

When a regulatory authority has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR, the MAH should summarize the result of the analysis in this section if it is negative.

10. Overall safety evaluation

10.1 Signal and risk evaluation

The purpose of this section is to provide:

- A succinct summary of what is known about important identified and potential risks and important missing information at the beginning of the reporting interval covered by the report
- An evaluation of all signals closed during the reporting interval
- An evaluation of new information with respect to previously recognized identified and potential risks
- An updated characterization of important potential and identified risks ,where applicable and
- A summary of the effectiveness of risk minimization activities in any country or region, which may have utility in other countries or regions.

These evaluations of subsections should not summarize or repeat information presented in previous sections of the PSUR, but should instead provide an interpretation of the information, with a view towards characterizing the profile of those risks assessed as important.

10.1.1 Summary of safety concerns

The purpose of this sub-section is to provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR. It should provide the following safety information:

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

The summary of important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the pharmaceutical product.

10.1.2 Signal evaluation

This sub-section of the PSUR should summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval.

A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation.

The description(s) of the signal evaluations can be included in this section of the PSUR, or in Appendix D. Each signal evaluation should include the following information as appropriate:

- Source of the signal
- Background relevant to the evaluation
- Method(s) of evaluation, including data sources, search criteria (wherever applicable, the specific coding terminology [e.g., PTs, HLTs, SOCs, etc.] or coding queries that were reviewed, and analytical approaches
- Results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an ICSR, (e.g., an index case of well documented agranulocytosis or Stevens Johnson syndrome)
- Discussion
- Conclusion

MAHs evaluations and conclusions for refuted signals should be supported by data and clearly presented.

10.1.3 Evaluation of risks and new information

This section should provide a critical appraisal of new information relevant to previously recognized risks that is not already included in the previous section.

Updated information on a previously recognized risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information that allows further characterization of a previously recognized risk.

New information can be organized as follows:

- New information on important potential risks
- New information on important identified risks
- New information on other potential risks not categorized as important
- New information on other identified risks not categorized as important
- Update on important missing information

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR. This should be concise and interpret the impact, if any, on the understanding and characterization of the risk. Wherever applicable, the evaluation will form the basis for an updated characterization of important potential and identified risks in Section (Characterization of risks). It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of new information and missing information update(s) can be included in this section of the PSUR, or in an Appendix. Each evaluation should include the following information as appropriate:

- Source of the new information
- Background relevant to the evaluation
- Method(s) of evaluation, including data sources, search criteria, and analytical approaches
- Results - a summary and critical analysis of the data considered in the risk evaluation
- Discussion
- Conclusion including whether or not the evaluation supports an update of the characterization of any of the important potential and identified risks.

10.1.4 Characterization of risks

This section will characterize important identified and important potential risks based on cumulative data (i.e., not restricted to the reporting interval), and describe important missing information.
Depending on the nature of the data source, the characterization of risk may include, wherever applicable:

- Frequency
- Numbers of cases (numerator) precision of estimate, taking into account the source of the data
- Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate
- Estimate of relative risk precision of estimate
- Estimate of absolute risk precision of estimate
- Impact on the individual patient (effects on symptoms, quality or quantity of life)
- Public health impact
- Patient characteristics relevant to risk (e.g., age, pregnancy/lactation, disease severity, hepatic/renal impairment, relevant co-morbidity, genetic polymorphism)
- Dose, route of administration
- Duration of treatment, risk period
- Preventability (i.e., predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker)
- Reversibility
- Potential mechanism
- Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable

10.1.5 Effectiveness of risk minimization (if applicable)

Risk minimization activities are public health interventions intended to prevent the occurrence of an ADR associated with the exposure to a pharmaceutical product or to reduce its severity should it occur. The aim of a risk minimization activity is to reduce the probability or severity of an ADR. Risk minimization activities may consist of routine risk minimization (e.g. product labelling) or additional risk minimization activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PSUR shall contain the results of assessments of the effectiveness of risk minimization activities relevant to the benefit- risk assessment.Relevant information on the effectiveness and/or limitations of specific risk minimization activities for important identified risks that has become available during the reporting interval should be summarized in this section.

Insights into the effectiveness of risk minimization activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarized by region, if applicable and relevant. When required for reporting in a PSUR, results of evaluations that are relevant to only one region and that became available during the reporting interval should be provided in regional Appendixes.

10.2 Benefit evaluation

10.2.1 Important baseline efficacy/effectiveness information

This section summarizes information on the efficacy/effectiveness of the pharmaceutical product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the pharmaceutical product listed in the reference product information

For pharmaceutical products with multiple indications, population, and/or routes of administration, the benefit should be characterized separately by these factors, wherever relevant. The level of detail provided in this section should be sufficient to support the characterization of benefit in PSUR and the benefit-risk assessment.

10.2.2 Newly identified information on efficacy/effectiveness

For some products new information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section. For the approved indications, new information on efficacy/effectiveness under conditions of actual use should also be described in this section, if available. New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the benefit-risk evaluation in the approved indication.

Information on additional indications approved during the reporting interval should also be included in this section. New information on efficacy/effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti-infective agents.

10.2.3 Characterization of benefits

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications. When there are no new

relevant benefit data, this sub-section should provide a characterization of the information in sub-section "Important baseline efficacy and effectiveness information".

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this sub-section should be succinct. This sub-section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following whenever available:

- A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across clinical trials/studies
- New information that challenges the validity of a surrogate endpoint, if used
- Clinical relevance of the effect size
- Generalisability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population
- Adequacy of characterization of dose-response
- Duration of effect
- Comparative efficacy
- A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice

10.3 Benefit-Risk analysis evaluation

This section should provide an integration and critical analysis of the key information. This section also provides the benefit-risk analysis, and should not simply duplicate the benefit and risk characterization presented in subsections mentioned above.

10.3.1 Benefit-Risk context - medical need and important alternatives

This sub-section should provide a brief description of the medical need for the pharmaceutical product in the approved indications, and summarize alternatives (medical, surgical, or other; including no treatment).

10.3.2 Benefit-Risk analysis evaluation

A benefit-risk balances specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible.

The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should take into account the following points:

- Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks

considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.

- Consider the context of use of the pharmaceutical product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.
- With respect to key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g., for therapies for arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit- risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
- Economic considerations (e.g., cost-effectiveness) should not be included in the benefit-risk evaluation.

Note : *When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis is warranted.*

Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

11. Conclusions

This section should provide a conclusion about the implications of any new information that arose during the reporting interval, in terms of the overall benefit-risk evaluation, for each approved indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data, and the benefit-risk analysis, the manufacturer and/or importer should assess the need for further changes to the reference product information and propose changes as appropriate. In addition and as applicable, the conclusion should include preliminary proposal(s) to optimize or further evaluate the benefit-risk balance, for further discussion with the relevant regulatory authorities. This may include proposals for additional risk minimization activities. These proposals should also be considered for incorporation into the RMP.

12. Appendix to the PSUR

A PSUR should contain the following appendix as appropriate:

- Reference Safety Information
- Current marketing authorization status
- Line listings of individual case histories
- Cumulative summary tabulations of SAEs from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
- Tabular summary of safety signals (if not included in the body of the report)
- Listing of all the marketing authorization holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the pharmaceutical product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.

MODULE 4

Quality Management System at Marketing Authorization Holder Organization

Contents:

4.1 Introduction

This module contains guidance for the establishment and maintenance of quality assured Pv system for MAHs for performing their Pv activities; MAHs shall establish and use quality systems that are adequate and effective for the performance of Pv activities.

4.2 Scope

This guidance document implies to all MAHs who hold marketing authorization to manufacture or import of pharmaceutical products in Indian market.

4.3 Structures and Processes

4.3.1 Pharmacovigilance system

A Pv system is defined as a system used by MAH to fulfil its legal tasks and responsibilities in relation to Pv and designed to monitor the safety of pharmaceutical products approved by appropriate licensing authorities in India and to detect any change to their benefit-risk balance. This system should cover MAHs organizational structure i.e. organogram describing Pv personnels' roles and responsibilities, procedures, processes and resources of the Pv system as well as appropriate resource management, compliance management and record management (Refer Module 1 for more details).

4.3.2 Quality cycle of Pv system

The quality system shall be based on all of the following activities:

- Quality planning: Establishing structures and planning integrated and consistent processes;
- Quality adherence: Carrying out tasks and responsibilities in accordance with quality requirements
- Quality control and assurance: Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out;
- Quality improvements: Correcting and improving the structures and processes wherever necessary

4.3.3 Quality objectives for Pv

The overall quality objectives of a Pv system are:

- Complying with the legal requirements for Pv tasks and responsibilities;
- Preventing harm from AEs in humans arising from the use of approved pharmaceutical products within or outside the terms of marketing authorization or from occupational exposure;
- Promoting the safe and effective use of pharmaceutical products, in particular through providing timely information about the safety of pharmaceutical product to patients, HCPs and the public;
- Contributing to the protection of patients and public health.

4.3.4 Responsibilities for the quality system within an organization

MAH shall have a sufficient number of competent and appropriately qualified and trained personnel for the performance of Pv activities.

For the purpose of a systematic approach towards quality in accordance with the quality cycle, managerial staff in the organization should be responsible for:

- Ensuring that the organization documents the quality system;
- Ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- Ensuring that adequate resources are available and that training is provided;
- Ensuring that suitable and sufficient premises, facilities and equipments are available;
- Ensuring adequate compliance management;
- Ensuring adequate record management;
- Reviewing the Pv system, including its quality system at regular intervals in risk based manner to verify its effectiveness and introducing corrective and preventive measures wherever necessary;
- Ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to pharmaceutical products within an organization;
- Identifying and investigating concerns arising within an organization regarding suspected non-adherence to the requirements of the quality and Pv system and taking corrective, preventive and escalation action as necessary;
- Ensuring that audits are performed;
- Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organization.

4.3.5 Training of MAH personnel for Pv

All personnel involved in the performance of Pv activities shall receive initial and continued training. This training shall relate to the roles and responsibilities of the personnel and start within one month of joining.

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

4.3.6 Facilities and equipment for Pv

Achieving the required quality for the conduct of Pv processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, Information Technology (IT) systems and storage space (electronic). They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for Pv.

Facilities and equipment which are critical for the conduct of Pv should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.

4.4 Specific quality system procedures and processes

4.4.1 Compliance management by MAH

For the purpose of compliance management, MAHs shall have specific quality system procedures and processes in place in order to ensure the following:

- Continuous monitoring of Pv data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAH (refer Module 6 for detailed information)
- Scientific evaluation of all information on the risks of pharmaceutical products as regards patients or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure (refer Modules 2, 3 and 6 for detailed information)
- Submission of accurate and verifiable data on all ADRs to the regulatory authority/NCC-PvPI, IPC within the legally required time-limits (refer Modules 2 and 6 for detailed information)
- Quality, integrity and completeness of the information submitted on the risks of pharmaceutical products, including processes to avoid duplicate submissions and to validate signals (refer Modules 2, 3, and 6 for detailed information)
- Effective communication with regulatory authority, including communication on new or changed risks, the PvMF (refer Module 1 for detailed information), risk management systems (refer Module 6 for detailed Information), PSURs (refer Module 3 for detailed information) and CAPAs (refer Modules 1& 5 for detailed information).

4.4.2 Record management

The MAH shall record all Pv information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information.

As part of a record management system, specific measures should, therefore, be taken at each stage in the storage and processing of Pv data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorized personnel respecting the medical and administrative confidentiality of the data. The hard copies should be retained for a minimum of 10 years and soft copies to be stored indefinitely.

4.4.3 Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures. For the requirements of documenting the quality system (refer module 1 for detailed information).

It is recommended that the documentation of the quality system also includes:

- Methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil

the quality objectives;

- A record management policy;
- Records created as a result of Pv processes which demonstrate that key steps for the defined procedures have been taken;
- Records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- Records to demonstrate that deficiencies and deviations from the established quality system are monitored, that CAPA have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

4.4.4 Critical Pv processes and business continuity

The following Pv processes should be considered as critical include:

- Continuous safety profile monitoring and benefit-risk evaluation of authorized pharmaceutical products;
- Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;
- Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of ICSRs from any source;
- Signal management;
- Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSURs;
- Meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- Interaction between the Pv and product quality defect systems;
- Communication about safety concerns between MAHs and licensing authority in particular notifying changes to the benefit-risk balance of pharmaceutical products;
- Communicating information to patients and healthcare professionals about changes to the benefit-risk balance of pharmaceutical products for the aim of safe and effective use of pharmaceutical products;
- Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the regulatory authority;
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required.

- Business continuity plans should be established in a risk-based manner and should include:
  - Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for Pv in particular; and
  - Back-up systems for urgent exchange of information within an organization, amongst organizations sharing Pv tasks as well as between MAHs and competent authorities

4.4.5 Monitoring of the performance and effectiveness of the Pv system and its quality system

Processes to monitor the performance and effectiveness of a Pv system and its quality system should include:

- Reviews of the systems by those responsible for management;
- Audits;
- Compliance monitoring;
- Inspections;
- Evaluating the effectiveness of actions taken with pharmaceutical products for the purpose of minimizing risks and supporting their safe and effective use in patients.

The organization may use performance indicators to continuously monitor the good performance of Pv activities in relation to the quality requirements. The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system at regular intervals, with the frequency and the extent of the reviews to be determined in a risk based manner.

Reviews of the quality system should include the review of SOPs and work instructions, deviations from the established quality system, audits and inspections reports as well as the use of the indicators referred to above.

4.4.6 Responsibilities of the MAH in relation to the PvOI for Pv

Refer Module 1 for detailed information .

MODULE 5

Audit & Inspection of Pharmacovigilance System at Marketing Authorization Holder Organization

Contents:

5.1 Introduction

This module provides insight into planning, conducting, reporting and follow-up of Pv inspections by regulatory authorities/officials responsible for inspection to improve/assure Pv process as per Pv guidance document for MAHs in India.

5.2 Objectives

The objectives of Pv audits and inspections are as below:

- To verify by examination and by evidence, the appropriateness and effectiveness of the implementation and operation of the Pv system, including its quality system for Pv activities
- To find evidence and help evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled and contributing to the improvement, control and governance of Pv processes.

Inspections broadly cover the following:

- To assess and establish that the MAH has qualified personnel, robust system and facilities to conduct Pv activities
- To identify, record and address non-compliance which may pose a risk to public health
- To take regulatory action wherever considered necessary based on the result of the inspections.

Pv inspection programmes will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate "for cause" inspections, which have been triggered to examine suspected non-compliance or potential risks, usually with impact on a specific product(s).

The results of an inspection will be provided to the inspected entity, who will be given the opportunity to comment on any non-compliance identified. Any non-compliance should also be rectified by the MAH within three months through the implementation of CAPA plan.

5.3 Inspection Types

To ensure that MAHs comply with Pv regulatory obligations and to facilitate compliance, regulatory authorities/officials responsible for inspection may conduct Pv inspections at the place where Pv activities are performed. Inspections can be routine as well as targeted to MAHs suspected of being non-compliant.

5.3.1 Routine inspection

These inspections are usually system inspections. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory Pv obligations for the marketed Pharmaceutical products in India. Regulatory authorities should determine a program for inspection in relation to marketed pharmaceutical products. These inspections will be prioritized based on the potential risk to public health, the nature of the products, the extent of use, number of products that the MAH has in Indian market.

5.3.2 Targeted inspections

Such type of inspection may be conducted as and when there is trigger and the regulatory authority determines that inspection is the appropriate way. Triggering factors for such type of inspections may be as below (but not limited to):

- Continuous delays or omission or poor quality reporting of ICSRs/PSURs/RMPs.
- Failure to provide the requested information or data within the deadline specified by regulatory authority
- Delays or failure to carry out specific obligations relating to the monitoring of pharmaceutical product safety, identified at the time of the marketing authorization
- Delays in the implementation or inappropriate implementation of CAPAs
- Sudden product withdrawal

5.4 Inspection Procedure

5.4.1 Inspection Planning

Pv inspection 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 and scope of inspections to be determined accordingly. Pv inspection may be done by the officials responsible for inspection.

Factors which may be taken into consideration, as appropriate, by the licensing authority when establishing Pv inspection programmes include, but are not limited to:

- Compliance history identified during previous Pv inspections or other types of inspections (GCP, GMP, GLP);
- Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection
- MAH with sub-contracted Pv activities (function of the qualified person responsible for Pv in India, reporting of safety data, etc.) and/or multiple firms employed to perform Pv activities;
- Changes to the Pv safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in contractual arrangements with Pv service providers or the organizations at which Pv is conducted;
- Delegation or transfer of PvMF management
- Change of PvOI since the last inspection

5.4.2 Organization to be inspected

Any party carrying out Pv activities in whole or in part, on behalf of, or in conjunction with the MAH may be inspected, in order to confirm their capability to support the MAH's compliance with Pv obligations.

5.4.3 Inspection procedures

The inspection procedures depend on the nature (routine/targeted) of the inspection and the conditions of inspection request. All the necessary Pv documents should be submitted to the inspectors during inspection. When necessary, the inspectors may also request other documents related to the inspection, including job descriptions of Pv personnel and company related information. They shall also conduct interviews of the relevant persons involved in different Pv activities. Inspection should be carried to examine compliance with Drugs and Cosmetics Act, 1940 and Rules 1945.

5.4.4 Inspection findings

Each inspection will result in an inspection report and the findings shall be classified into critical, major and minor. The inspection report will be made available to the Pv department of MAH.

Critical: Fundamental weakness in the Pv systems or practices that adversely deviate from the Pv regulations and/or affect the rights and safety of patients, or poses a potential risk to public health.

Major: It's a significant weakness in one or more Pv processes or practices, or a fundamental weakness in part of one or more Pv processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious

Minor: It's a weakness in the part of one or more Pv processes or practices that is not expected to adversely affect the whole Pv system or process and/or the rights, safety or well-being of patients

5.4.5 Inspection follow-up

When non-compliance with Pv obligations is identified during an inspection, follow-up will be required until a CAPA is completed. The following follow-up actions should be considered, as appropriate:

- Review of the MAH's CAPA plan;
- Review of the periodic progress reports, when deemed necessary;
- Re-inspection to assess appropriate implementation of the corrective and preventive action plan;
- Requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;
- Requests for issuing safety communications, including amendments of marketing and/or advertising information;
- Communication of the inspection findings to other regulatory authorities (including outside India);
- Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorizations or clinical trial authorizations).

5.4.6 Responding to inspection findings

The inspection findings and the report should be effectively communicated to the operations teams for effective correction of the flaws identified. Corrective measures should be carried out by the operations team and documented, whose supporting documentary evidences should be provided in records to inspectors. A closure report should be communicated to key stakeholders. List of inspections to be conducted and completed with documentary evidences should be included in the PvMF document.

5.5 Regulatory actions

When non-compliance with Pv regulatory 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:

- Suspension/Cancellation/Withdrawl of Marketing authorization.
- Restriction on approvals of new marketing authorization applications.
- Product recalls.
- Updation of package inserts/SmPCs

5.6 Training of Inspectors

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 Pv processes and requirements in such a way that they are able, if not acquired by their experience, to comprehend the different aspects of a Pv system.

Documented processes should be in place in order to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of Pv legislation and guidance.

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

MODULE 6

Submission of Risk Management Plan

Contents:

6.1 Introduction

At the time of authorization, information on the safety of a pharmaceutical product is relatively limited as the clinical studies are carried out in the relatively small numbers of subjects compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

A pharmaceutical product is authorised on the basis that in the specified indication(s), at the time of authorization, the benefit-risk balance is judged to be positive for the target population. A pharmaceutical product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorization is sought and many of the risks associated with the use of a pharmaceutical product will only be discovered and characterised post-marketing.

The overall aim of risk management is to ensure that the benefits of a particular pharmaceutical product (or a series of pharmaceutical products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (including those linked to the safety specification section on missing information) and their integration, wherever necessary, in the RMP may enable resources to be used more efficiently and for risks to be put into context.

6.2 Objectives

- Identify or characterize the safety profile of the pharmaceutical product(s) concerned;
- Indicate how to characterize further the safety profile of the pharmaceutical product(s) concerned;
- Document measures to prevent or minimize the risks associated with the pharmaceutical product, including an assessment of the effectiveness of those interventions;
- Document post-marketing obligations that have been imposed as a condition of the marketing authorization

The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the pharmaceutical products. The RMP of every product shall be approved by the regulatory authority and should be updated as and when required (for a new safety concern or regulatory recommendation).

To fulfil above objectives a RMP should also:

- Describe what is known and not known about the safety profile of the concerned pharmaceutical product(s);
- Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-marketing phase (also known as effectiveness studies);
- Include a description of how the effectiveness of risk minimization measures will be assessed (if any)

6.3 Content of RMP

The risk management plan details the Pv activities and risk minimization activities which will be taken to reduce the risks associated with an individual safety concern.

RMP should contain following sections:

6.3.1 Pharmaceutical product overview

The MAH should provide an overview of the pharmaceutical product including:

- **Active substance information:-** the active substance(s), name of MAH, date and country of first launch/authorization worldwide (if applicable), chemical class, indication (s), mechanism of action, dosage, pharmaceutical form and strength.
- **Administrative information on the RMP:** data lock point, date submitted and version number of all parts RMP.

6.3.2 Safety specifications

The MAH should provide a synopsis of the safety profile of the pharmaceutical product(s) and should include what is known and not known about the pharmaceutical product(s) safety. The safety specification consists of following subsections:

6.3.2.1 Epidemiology of the indication(s) and target population(s):

This section should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin.

6.3.2.2 Non-clinical part of the safety specification:

This section should present a summary of the important non-clinical safety findings like toxicity related information, interactions, etc.

6.3.2.3 Clinical trial exposure:

This section includes the data on the patients studied in clinical trials. This should be stratified for relevant categories (age, gender, indication, ethnicity, exposure to special population) and also by the type of trial (randomized blinded trial population only and all clinical trial population).

6.3.2.4 Populations not studied in clinical trials:

This section discusses which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. Populations to be considered for discussion should include, but might not be limited to, paediatric population, geriatrics population, pregnant/lactating women, hepatic/renal impairment patients etc.

6.3.2.5 Post-marketing experience:

This section should provide information on the number of patients exposed during post-marketing; how the

pharmaceutical product has been used in practice and labelled and off-label use including use in the special populations mentioned above. This should also include any action taken by any regulatory authority/MAH for safety reason.

6.3.2.6 Identified and potential risks:

This section provides information on the important identified and potential risks associated with the use of the Pharmaceutical product. These should include only the important identified and potential Adverse Events/Reactions, important identified and potential interactions with other pharmaceutical products, foods and other substances, and the important pharmacological class effects.

The risk data should include frequency, public health impact, risk factors, preventability, potential mechanism, evidence source/strength.

6.3.2.7 Summary of the safety concerns:

At the end of the RMP part "Safety specification" a summary of the safety concerns should be provided .

6.3.3 Pv activities

MAH should list the various Pv activities involved to identify a new safety concern or further characterization of known safety concerns or investigation of potential safety concern is real or not, how missing information will be sought. Pv activities can be divided into routine Pv activities and additional Pv activities. For each safety concern, the MAH should list their planned Pv activities for that concern. Pv plans should be proportionate to the risks of the product. If routine Pv is considered sufficient for post-marketing safety monitoring, without the need for additional actions (e.g. safety studies) "routine Pv" should be entered against the safety concern.

6.3.4 Risk minimization activities

The MAH should have the updated SmPC, the labelling, PIL, the pack size, the schedule category as routine risk minimization activities. The MAH should also consider when appropriate to have additional Risk minimization activities like education material, communication letter to HCPs etc.

For each safety concern, the following information should be provided:

- Objectives of the risk minimization activities;
- Routine risk minimization activities;
- Additional risk minimization activities (if any), individual objectives and justification of why needed;
- How the effectiveness of each (or all) risk minimization activities will be evaluated in terms of attainment of their stated objectives;
- What the target is for risk minimization, i.e. what are the criteria for judging success;
- Milestones for evaluation and reporting.

REFERENCES:

1. Drugs and Cosmetics Act, 1940 and Rules, 1945- Schedule Y
2. PvPI Guidance Document
3. Guidance for Industry on Pharmacovigilance Requirements for Biological Products-CDSCO
4. ICH Guideline: E2E : Pharmacovigilance Planning
5. ICH-E2C (R2): Periodic Benefit-Risk Evaluation Report
6. ICH-E2D: Post-Approval Safety Data Management: Definition in Standards for Expedited Reporting
7. ICH-E3 : Structure and Content of Clinical Study Report
8. Good Pharmacovigilance Practices (GVP) of European Union
9. WHO- UMC: Global Pharmacovigilance

APPENDIXES:

Appendix-A:

"Simplified E2B Guide for Primary Reporters" document id 01-15-006; Version 1.1 by WHO-UMC (Available online at www.ipc.gov.in).

Appendix B:

WHO-UMC causality assessment scale

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Appendix C:

Example of summary tabulations

Note: *These examples can be modified by manufacturer and/or importer to suit specific situations, as appropriate.*

Table 01: Estimated cumulative subject exposure from clinical trials

Treatment	Number of Subjects
Pharmaceutical product	
Comparator	
Placebo	

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomization schemes for ongoing trials.

Table 02: Cumulative subject exposure to new drug from completed clinical trials by age and sex*

	Number of Subjects		
Age Range	Male	Female	Total

Table 03: Cumulative subject exposure to new drug from completed clinical trials by racial/ethnic group*

Racial/Ethnic group	Number of Subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

*Data from completed trial as of [date]

Table 04: Cumulative exposure from marketing experience from India

Indication	Sex		Age				Dose (mg/day)			Formulation		
	Male	Female	≥ 16 to 16	>16 to 65	>65	unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others
Overall												
Depression												
Migraine												

includes cumulative data obtained from month/day/year through month/day/year, where available

Table 05: Interval exposure from marketing experience from India

Indication	Sex		Age				Dose (mg/day)			Formulation		
	Male	Female	≥ 16 to 16	>16 to 65	>65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others
Depression												
Migraine												

includes interval data obtained from month/day/year through month/day/year, where available

Table 06: Cumulative exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose (mg/day)			Formulation			RoW (within zone applicable)				
	Male	Female	≥ to 16	>16 to 65	>65	unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others	EU	Japan	Mexico	USA/Canada	Other
Overall																	
Depression																	
Migraine																	

includes cumulative data obtained from month/day/year through month/day/year, where available

Table 07: Interval exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose (mg/day)			Formulation			ROW (drop down if not applicable)				
	Male	Female	2 to 16	>16 to 65	>65	unknown	<=40	>40	Unknown	Intravenous	Oral	Others	EU	Japan	Mexico	US/Canada	Other
Depression																	
Migraine																	

includes interval data obtained from month/day/year through month/day/year, wherever available

Table 08: Cumulative tabulations of Serious Adverse Events from clinical trials

System Organ Class	Investigational Pharmaceutical product	Blinded	Active comparator	Placebo
Preferred Term				
Blood and lymphatic system disorders				
Anaemia				
Bone marrow necrosis				
Cardiac disorders				
Tachycardia				
Ischemic cardiomyopathy				

Table 09: Numbers of ADRs by term from Post-Marketing Sources

	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and report from other solicited sources	
	Serious		Non serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
SOC 1							
PT							
SOC 2							
PT							

Appendix D:

Tabular Summary of Safety Signals that were ongoing or closed during the reporting Interval (Reporting Interval: DD-MM-YYYY to DD-MM-YYYY)

Signal term*	Date detected@	Status (ongoing or closed)#	Date closed (for closed signals)$	Source of signal**	Reason for evaluation & summary of key data@@	Method of signal evaluation	Action(s) taken or planned##
Stroke	MM/YYYY	Ongoing	MM/YYYY	Meta analysis (published paper)	statistically significant increase in frequency	review meta analysis and available data	pending
SJS	MM/YYYY	Closed	MM/YYYY	Spontaneous case reports & clinical signal in Phase IV trial	Not already an identified risk. SJS not reported in pre-authorization CTs. 3 apparently unconfounded reports within 6 months of approval [illegible]	Targeted follow-up of reports with [illegible]. Full analysis of cases by manufacturer and/or importer [illegible]	RSI updated with a Warning and Precaution; DHPC and/or [illegible]; Effectiveness survey planned 6 months post DHPC; RMP updated

**Signal term:* A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific term(s), depending on the source of signal.*

*@ **Date detected (month/year):** Month and year the manufacturer and/or importer became aware of the signal.*

*# **Status:** Ongoing: Signal under evaluation at the data lock point of the PSUR. Provide anticipated completion date, if known; closed: Signal for which evaluation was completed before the data lock point of the PSUR*

***Note:** A new signal of which the manufacturer and/or importer became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR.*

*$ **Date closed (month/year):** Month and year when the signal evaluation was completed.*

*** **Source of signal**: Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous Adverse Event Reports, clinical trial data, scientific literature, non-clinical study results, or information requests or inquiries from a regulatory authority.*

*@@ **Reason for evaluation**: A brief summary of key data and rationale for further evaluation.*

*## **Actions taken or planned:** State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed. Otherwise leave blank for ongoing signals.*

Appendix E:

PSUR Summary Report Checklist

Checklist to be completed and accompany a PSUR report as depicted below:

	Periodic Safety Update Report (PSUR) Checklist	Description	Status	Page No.
1	Product for which PSUR submitted			
1.1	Biologics			
1.2	Therapeutic Product			
1.3	Fixed Dose Combinations			
1.4	Other			
2	PSUR submitted To			
2.1	CDSCO			
2.2	NCC-PvPI, IPC			
2.3	AEFI			
3	Reason for PSUR Submission			
3.1	Significant change in what is known about the risks and benefits			
3.2	Requested Periodic			
3.3	Requested Ad-Hoc			
3.4	Voluntary	List reasons (eg. New safety information)		
4	Status in India			
4.1	Marketed (since)			
4.2	Not-marketed			
5	PSUR information			
5.1	Executive summary			
5.2	Date of marketing authorization			

5.3	Period covered by the present PSUR			
5.4	Period covered by the previous PSUR			
6	[illegible]			
6.1	Reference Safety Information			
6.2	Cumulative summary tabulation of serious AEs from clinical trials and interval/cumulative summary tabulations from marketed experience			
6.3	Tabular summary of safety signals			
6.4	Listing of interventional and non-interventional studies with a primary objective of post-marketing safety monitoring			
6.5	List of the sources of information used to prepare the PSUR			

Appendix F:

Definitions:

Adverse Drug Reactions (ADR)	A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972)
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Benefit - risk analysis	Examination of the favourable (beneficial) and unfavourable results of undertaking a specific course of action. (While this phrase is still commonly used, the more logical pairings of benefit harm and effectiveness-risk are slowly replacing it).
Causality assessment	The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according to established algorithms.
Company Core Data Sheet (CCDS)	A document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.
Company Core Safety Information (CCSI)	All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected ad unexpected are determined for expedited reporting.
Clinical trial	A systematic study on pharmaceutical products on human subjects (whether patients or non-patient volunteers) in order to discover or verify the clinical, pharmacological (including pharmacodynamics/ pharmacokinetics) and/or adverse effects, with the objective of determining their safety and/or efficacy.
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the pharmaceutical product of interest. Examples of identified risks include: • An adverse reaction adequately demonstrated in nonclinical studies and confirmed by clinical data; • An adverse reaction observed in well designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship; and an adverse reaction suggested by a number of well • An adverse reaction suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Individual Case Safety Report (ICSR)	A report that contains information describing a suspected ADR related to the administration of one or more pharmaceutical products to an individual patient.
Investigational drug	The term investigational drug is used in this guideline to indicate only the experimental product under study or development
New Drug	According to Rule 122E: For the purpose of this part, new drug shall mean and include- [(a) A drug, as defined in the Act including bulk drug substance [or phytopharmaceutical drug] which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognized as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims: Provided that the limited use, if any, has been with the permission of the licensing authority.] (b) A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration. (c) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration. Explanation.- For the purpose of this rule– (i) all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority under Rule 21; (ii) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval
Marketing Authorization Holder (MAH)	For the purpose of this guidance document, Marketing Authorization Holder (MAH) refers to the manufacturer or the importer of the drug, who has valid manufacturing or import license.
Post-marketing	The stage when a drug is generally available on the market.
Potential Risk	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. Examples of potential risks include: non-clinical safety concerns that have not been • Observed or resolved in clinical studies; adverse events observed in clinical trials or • Epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship; an event which is known to be associated with other • Products of the same class or which could be expected to occur based on the properties of the medicinal product.

PSUR	The Periodic Safety Update Report (PSUR) is a stand-alone document that allows a periodic but comprehensive assessment of the worldwide safety data of a pharmaceutical product.
Reference Safety Information (RSI)	All relevant safety information contained in the reference product information (e.g., CCDS) prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is a subset of information contained within the MAH's reference product information for the PBRER. Where the reference product information is the Company Core Data Sheet (CCDS), the reference safety information is the Company Core Safety Information (CCSI).
Serious Adverse Event	A serious adverse event or reaction is any untoward medical occurrence that at any dose: • results in death • results in life-threatening condition • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • is a congenital abnormality/birth defect
Side effect	Any unintended outcome that seems to be associated with treatment, including negative or positive effects. This term has come to be used exclusively in the sense of 'adverse effect'; this loses the important dimension of potential reference to unintended positive effects as well as linguistically masking the adverse element of a negative side effect.
Solicited reports	Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.
Spontaneous Report	An unsolicited communication to a company, regulatory authority, or other organization that describes an ADR in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.
Signal	Information that arises from one or multiple sources (including observations and experiments), that 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 further action to verify.
Summary of Product Characteristics	A regulatory document attached to the marketing authorization which forms the basis of the product information made available to prescribers and patients.

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