Pharmacovigilance Guidance Document

for

Marketing Authorization Holders of Pharmaceutical Products

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

DISCLAIMER

The Pharmacovigilance Guidance Document for Marketing Authorization Holders (MAHs) 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 the Drugs and Cosmetic Act, 1940 & Rules, 1945 or any other relevant Act and are subject to being in conformity with the Drugs and Cosmetic Act, 1940 & Rules, 1945 including New Drugs & Clinical Trials Rules, 2019 (NDCT Rules, 2019) as amended from time to time.

This document facilitates MAHs to set up a Pharmacovigilance System at their organization as per the recent amendment in Drugs and Cosmetic Act, 1940 & Rules, 1945. This document will help in uniformity of Pharmacovigilance System in India, Preparation of Pharmacovigilance System Master File by MAHs, Post Marketing Surveillance of Pharmaceutical Products, Preparation & Submission of Periodic Safety Update Report (PSUR), Quality Management System (QMS) at MAH site, Audits and Inspection of Pharmacovigilance System at MAH site and submission of Risk Management Plan by MAH. In the event of any dispute as regard to the content of this document and the statues, the statutory provisions shall prevail. In case, there is an anomaly between the content of this document and any other statutory/official document, the decision of the Government of India or the implementing authority shall prevail.

PREFACE

This Pharmacovigilance Guidance Document for MAHs of Pharmaceutical Products in India is in accordance with the objective of Drugs and Cosmetics Act, 1940 & Rules, 1945 including NDCT Rules 2019. This guidance document is prepared by the National Coordination Centre (NCC)-Pharmacovigilance Programme of India (PvPI), Indian Pharmacopoeia Commission (IPC) in collaboration with Central Drugs Standard Control Organization (CDSCO) to facilitate submission of the safety profile of drugs by MAHs involved in the manufacture, sale, import and distribution of pharmaceutical products in India.

This guidance document defines the roles & responsibilities of CDSCO, State(s)/UT(s) Drugs Controller, NCC-PvPI, IPC and MAHs in preparation of Pharmacovigilance System Master File by MAHs, Post Marketing Surveillance of Pharmaceutical Products, Preparation & Submission of Periodic Safety Update Report (PSUR), Quality Management System (QMS) at MAH site, Audits and Inspection of Pharmacovigilance System at MAH site and submission of Risk Management Plan, wherever applicable. This guidance document also provides assistance to MAHs on establishing and ensuring an effective Pharmacovigilance System at their site. This guidance document may be amended from time to time after obtaining necessary approvals from the concerned authorities.

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1. 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
CAPA	Corrective And Preventive Action
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
EUA	Emergency Use Authorization
FDA	Food and Drugs Administration
GoI	Government of India
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HQ	Head Quarter
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IPC	Indian Pharmacopoeia Commission
MAHs	Marketing Authorization Holders
MoH&FW	Ministry of Health & Family Welfare
NCC	National Coordination Centre

NRA	National Regulatory Authority
PBRER	Periodic Benefit-Risk Evaluation Report
PIL	Prescribing Information Leaflet
PMS	Post Marketing Surveillance

PSUR	Periodic Safety Update Report
PT	Preferred Term
PvPI	Pharmacovigilance Programme of India
PV	Pharmacovigilance
PSMF	Pharmacovigilance System Master File
PVOIC	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 Territory
WHO	World Health Organization
XML	Extensible Markup Language

2. Introduction

India is one of the largest producers of quality medicines and also has robust Pharmacovigilance System to monitor the safety profile of marketed pharmaceutical products. The Ministry of Health & Family Welfare (MoH&FW), Government of India re-casted Pharmacovigilance Programme of India shifting the National Coordination Centre at Indian Pharmacopoeia Commission in April 2011. NCC-PvPI, IPC is receiving Individual Case Safety Reports (ICSRs) from the stakeholders including Marketing Authorization Holders across the country. This guidance document facilitates MAHs to setup & implementation of uniform Pharmacovigilance System for pharmaceutical products in the Indian market in post-licensure period.

This guidance document uses the following key terms;

Pharmacovigilance (PV):

PV defined as science and activities relating to the detection, collation, assessment, understanding and prevention of Adverse Event (AE) or any other drug related problem.

Marketing Authorization Holders (MAHs):

MAHs refers to the manufacturer or the importer of the drug, who has valid manufacturing or import licence.

After marketing authorization of new drug, the safety profile may show variation from that in clinical trial from patient to patient and therefore, MAH has to be carefully monitored for a specific period to submit the PSUR. As per the Drugs and Cosmetics Act, 1940 & Rules, 1945 including NDCT Rules, 2019, the PSURs are required to be submitted every six months for first two years from the date of approval and for subsequent two years annually. The Licensing Authority may extend the total duration of submission of PSUR, if it is considered necessary in the interest of public health.

In some specific condition, the early introduction of a new drug/vaccine is permitted, even if the complete clinical trial data as per the approved protocol is not available. This is based on the careful assessment of expected benefit & potential risk from limited number of subjects/patients. This is often referred to as Emergency Use Authorization (EUA). In COVID-19

pandemic, several vaccines and drugs were approved under EUA. In EUA, it is imperative that each EUA case is meticulously followed for any AE.

Thus, the reporting of any AE is important for continued risk-benefit evaluation of drug. This guidance document provides critical information for reporting AE by MAHs without any failure, accurately within stipulated time to NCC-PvPI, IPC and National Regulatory Authority (i.e. CDSCO).

This guidance document does not deal with medical devices and veterinary products.

a) Objectives

The Pharmacovigilance Guidance Document for MAHs has the following objectives;

1. To assist and facilitate MAHs of pharmaceutical products for reporting all AEs accurately, efficiently and timely to NCC-PvPI, IPC and CDSCO.
2. To establish a uniform PV System at MAHs site across the country by;
    - Preparation of Pharmacovigilance System Master File
    - Collecting, Processing and Reporting of Individual Case Safety Report (ICSR) by Marketing Authorization Holder (MAH)
    - Preparation & Submission of Periodic Safety Update Report by MAH
    - Implementation of Quality Management System at MAH site
    - Audits & Inspections of Pharmacovigilance System at MAH site
    - Preparation and Submission of Risk Management Plan

b) Scope

The scope of document covers the following category of pharmaceutical products:

- Drugs, New Drugs and Subsequently approved drugs
- Biologics including Biosimilars, Vaccines, Cell lines/culture-based products etc. (Refer "Guidance for industry on PV Requirements for Biological Products" by CDSCO for vaccines along with this guidance documents)
- Radiopharmaceuticals
- Phytopharmaceuticals Products

3. Role & Responsibilities of Different Authorities

In the context of Pharmacovigilance of Pharmaceutical Products, following are the authorities: -

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, enforcement of 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 1940 and Rules 1945, their under.

The Drugs Controller General of India, DCG(I), is the chairman of the steering committee of Pharmacovigilance Programme of India. The CDSCO receives the drug safety related recommendation from the PvPI for taking appropriate regulatory actions.

The 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.

As a condition of the marketing authorization, the MAH is also required to submit 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. Based on review, regulatory decisions are taken by CDSCO on safety and efficacy of the pharmaceutical products.

CDSCO is responsible to take appropriate regulatory decision on the basis of recommendations of Signal Review Panel (SRP) of NCC-PvPI. CDSCO is also responsible to take regulatory decisions on the basis of analysis of the PSUR data. Evidence-based information is utilized for appropriate regulatory decisions by the CDSCO such as changing/updating Prescribing Information Leaflet (PIL), issuing drug alerts, and signals, etc. if any.

Licensing Authority:

Drugs fall under the Concurrent List of the 7th Schedule of Constitution of India. Drugs & Cosmetics Act is a Central Act enforced both by the Central and State Governments. Every State and Union Territory of India has its own Drugs Regulatory Authorities. The State Drugs Controllers are primarily responsible for licensing of manufacturing and sale/distribution of drugs.

As per the requirements under sub para (2) of Schedule M (Good Manufacturing Practices and requirements of premises, plant and equipment for pharmaceutical products) of Drugs and Cosmetics Act 1940 and Rules 1945 there under mentioned as under, "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."

It is required under Rule that MAH should monitor Adverse Drug Reactions/ complaints related to the drugs marketed in the country and report to the Licensing authority. The MAHs are also encouraged to report all adverse events to NCC-PvPI (IPC).

National Coordination Centre-Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission

Pharmacovigilance Programme of India was operationalized in July, 2010 by Ministry of Health and Family Welfare (MoHFW), Government of India with a mission to safeguard the health of Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use. The AIIMS, New Delhi was established as National Coordination Centre (NCC) for PvPI. Later on, MoHFW, GoI on 15th April 2011, recasted this programme and shifted the NCC from AIIMS, New Delhi to Indian Pharmacopoeia Commission (IPC), Ghaziabad.

IPC was created to set standards of drugs in the country. Its basic function is to regularly update the standards of drugs. The standards of drugs are updated by adding new and revising the existing monographs through Indian Pharmacopoeia (IP). It further promotes rational use of medicines by publishing National Formulary of India (NFI).

The IPC as a National Coordination Centre (NCC) for PvPI has been working in collaboration with national and international stakeholders, ensuring patient's safety by monitoring ADRs. The NCC-PvPI, IPC also participates in the Programme for International Drug Monitoring by contributing ADRs to Uppsala Monitoring Centre (UMC), Sweden, a WHO-collaboration Centre. NCC-PvPI is also working as a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services since, July 2017.

The PvPI has succeeded in establishing AMCs across the major parts of 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 coordinating with Public Health Programmes (PHPs) such as National Tuberculosis Elimination Programme (NTEP), National Aids Control Programme (NACP) and National Centre for Vector-Borne Diseases Control (NCVBDC).

There are following expert's panels/committees under PvPI: -

- Steering Committee
- Working Group
- Signal Review Panel
- Core Training Panel
- Quality Review Panel

The PvPI has a system to collect, collate and analyze drug safety data from Indian population, which is submitted to CDSCO for appropriate regulatory decision, States/UTs drug regulatory authorities to promote and protect public health.

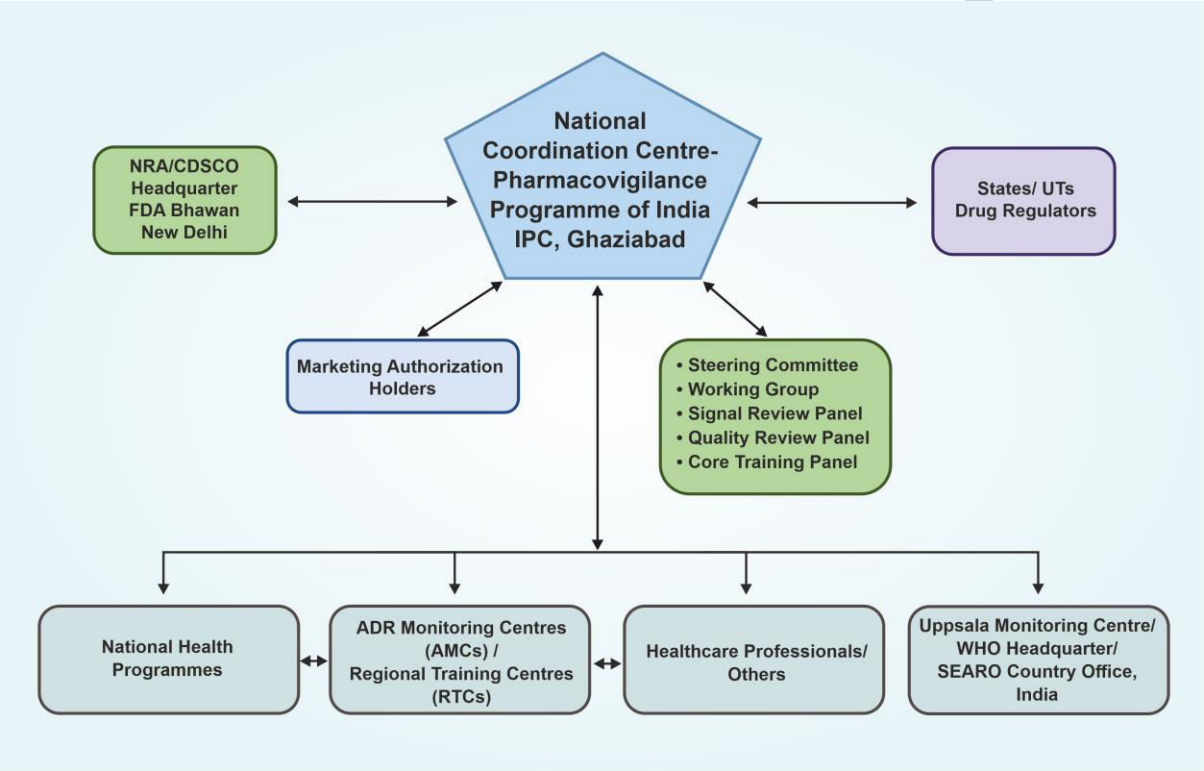

Figure I : PvPI-Programme Communication

B. CHAPTERS

Chapter 1 - Pharmacovigilance System Master File

Chapter 2 - Collection, Processing & Reporting of Individual Case Safety Report

Chapter 3 - Preparation & Submission of Periodic Safety Update Report

Chapter 4 - Quality Management System at MAH's organization

Chapter 5 - Audits and Inspections of Pharmacovigilance systems at MAH's Organization

Chapter 6 - Submission of Risk Management Plan

CHAPTER 1

Pharmacovigilance System Master File (PSMF)

Contents:

Pharmacovigilance System Master File

1.1 Introduction

The Pharmacovigilance System Master File (PSMF) provides a description of the pharmacovigilance system used by the MAH with respect to pharmaceutical products marketed by them. The PSMF is not a part of the marketing authorization (MA) dossier and is maintained independently from the MA.

1.2 Scope

The scope of this chapter is to provide guidance for MAH to create and maintain the PSMF at their site. This describes the different documents to be created, updated, controlled, archived and traceable, whenever required.

1.3 Contents of the PSMF

The PSMF should contain all information related to MAH's PV system and cover the following sections:

1.3.1 Pharmacovigilance personnel and their responsibilities: -

A qualified and trained personnel should be authorized by the company management as Pharmacovigilance Officer In-charge (PVOIC) with responsibilities for dealing PV activities at MAH's organization. The PVOIC should be a medical or pharmacy professional trained in the collection and analysis of AE reports. The PVOIC 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 PVOIC should reside in India and respond to queries of regulatory authorities including PvPI, IPC whenever required. The information related to the PVOIC provided in the PSMF should include:

•Contact details (Name, address, phone, e-mail);

•Summary, curriculum vitae with the key information on the role of the PVOIC;

•A description of the responsibilities guaranteeing that the PVOIC has sufficient authority over the PV system in order to promote, maintain and improve compliance;

•Details of Person-in-charge to work in the absence of PVOIC;

1.3.2 Pharmacovigilance Organization Structure

1.3.2.1 Marketing Authorization Holder

The Pharmacovigilance system organogram at MAH site should be included in the PSMF. The authorized signatory should be clearly indicated. The description of PV system at MAH site should be provided in PSMF.

1.3.2.2 Contract Research Organization

If, MAH assigns the responsibilities of PV activities of their pharmaceutical products to any CRO, then the information of the company(ies) including their allied PV departments involved and the relationship(s) between Contract Research Organizations & operational units relevant to the fulfilment of PV obligations should be provided. It should include:

- ❖ The PV organizational structure of the CRO's showing the organogram of the PV department.;
- ❖ Name & address of the organization, where the PV functions are undertaken such as collection of AEs, ICSRs processing, preparation & submission of PSURs, signal detection, Risk Management Plan (RMP), post-marketing surveillance and management of safety variations;
- ❖ Delegated activities (contracts and agreements);
- ❖ Service providing system (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 and validation etc.)

1.3.3 Sources of safety data

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

- Medical information inquiries;
- "Contact us" emails, website inquiry forms and helpline etc.;
- Pharmaceutical Product market complaints-Receipt, handling and disposal;
- MAH employees involved in PV activities;
- Spontaneous information from patient or their care givers and follow up of information;
- Published literature;
- Spontaneous reporting by HCPs;
- Reports from internet, digital media or social media;
- Patient-support programmes;
- Reports from National Regulatory Authorities;
- Contract partners involved in PV activities;

1.3.4 Pharmacovigilance Processes

1.3.4.1 Description

A description and flow-diagram of the entire PV process, data handling, records control and archives of PV performance and covering the following aspects should be included in the PSMF:

- The procedures for ICSR collection, collation, processing, assessment, reporting and follow-up; should clarify the activities;
- Compilation of all ICSR and preparation & submission of PSURs of new drugs in accordance with the New Drugs and Clinical Trials Rules, 2019 as amended from time to time;
- Review of ICSR, detection of signal (if any), Drug Safety Alerts, CAPA;
- Communication of Drug safety concerns to Consumers, HCPs, PvPI and the National Regulatory Authorities;
- SmPCs and PILs with history of revisions

1.3.4.2 SOPs 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, evaluations 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 & inspections;
- Quality Control for PV activities;

1.3.4.3 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 PSMF. 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 the data.

1.3.4.4 QMS in Pharmacovigilance

The 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 Adverse Events reported.
- **Trainings:** A summary of trainings records and files should be available at the PV site of MAH. 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/facilitate 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 findings, the date it was identified and the anticipated resolution

date(s) with cross reference to the audit report and the documented CAPA plan(s).

1.3.5 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.

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

- 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.

1.4 Annexures to the PSMF

- A list of pharmaceutical products including the name of the pharmaceutical product, active substance(s) and excipients;
- A list of contract agreements covering delegated activities including the pharmaceutical products;
- A list of tasks delegated by the PVOIC for PV;
- A list of all completed audits (regulatory as well as internal) and a list of audit schedules.

CHAPTER-2

Collection, Collation, Processing & Reporting of Individual Case Safety Reports

Contents:

2.1 Introduction

This section highlights the general principles for the Collection, Collation, Processing & Reporting of Individual Case Safety Reports associated with pharmaceutical products for human use.

2.2 Structure & Processes

2.2.1 Collection and Collation of ICSR

The MAHs will collect the Adverse Events of their marketed pharmaceutical products from different sources. The following sources/methods required to be established by MAHs to strengthen spontaneous reporting.

2.2.1.1 Medical inquiries

The MAHs should have a process in place to record all the medical inquiries related to their pharmaceutical products and documents including follow-up information or clarifications with a patient/consumer or HCPs. For inquiries that relate to safety of the pharmaceutical product, MAHs should ensure that there is a mechanism in place to transfer details of such cases to the PV point of contact.

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

The MAH should consider the mechanism(s) by which incoming information via "Contact us" on their MAH portal, through e mail addresses and 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 the 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 the information received and data collected from the various

sources. These employees should be well versed in dealing with the information i.e., how to report particular Adverse Events? The data captured manually by the medical representative during a discussion with 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 could be different types of contractual arrangements existing in the pharmaceutical industry like loan licensing, contract manufacturing, distribution etc. The responsibilities regarding PV activities among partners should be clearly defined in a drug safety data exchange agreement. Contractual partners are a potential source of ICSR and mechanisms should be in place for the exchange of these ICSR in an appropriate manner & timeframe to meet regulatory requirements.

2.2.1.5 Information on Adverse Events from the internet or digital media

The MAHs should regularly screen relevant websites or digital media (including newspapers) or social media under their management or responsibility for potential reports of Adverse Events. 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 of the information was posted on the website/digital media. MAHs may also consider utilizing their websites/portals to facilitate the collection of Adverse Events.

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 Adverse Events. Patient identity should be kept confidential.

2.3 Literature Monitoring

The scientific and medical literature is a significant source of information for monitoring the safety and benefit-risk profile of pharmaceutical products,

particularly in relation to the detection of new safety signals or emerging safety issues. MAHs should perform monthly literature review of their pharmaceutical products by using electronic literature data base (such as PubMed, Science Direct, Scopus etc.). Any AE identified by this process need to be processed as per spontaneous ICSR. The MAHs are advised to submit ICSR to NCC-PvPI along with the complete literature reference including Digital Object Identifier (DOI) or copy of full-length article, wherever feasible.

2.4 Follow-up of ICSR

When initial ICSR is received, the information on Adverse Event may be incomplete. Thus, the ICSR should be followed up as necessary to obtain the required information (Refer section 2.6.1, Essential data element of ICSR) required for clinical evaluation of the ICSR.

For serious ICSRs, at least two follow-up attempts must be made and documented. For non-serious ICSRs, at least one follow-up attempt must be made and documented. While reporting to PvPI, the MAH should clearly indicate that the reported ICSR is either initial or follow up.

2.5 Processing of ICSR

2.5.1 ICSR receipt

2.5.1.1 Date of receipt

The MAH should record the date of receipt for each Adverse Events; this applies to both initial notification and any follow-up communication.

2.5.1.2 Validation of reports

All reports of Adverse Events should be validated by authorized signatories of MAHs before reporting them to the NCC-PvPI, IPC & National Regulatory Authority.

2.6 Reporting of ICSR

Only valid ICSR would qualify for reporting to NCC-PvPI & National Regulatory Authority. Each valid ICSR should have the following minimum criteria for reporting: -

1. An identifiable patient (one or more identifier such as, patient initial, age, gender, weight);

2. An Adverse Event

3. A suspected pharmaceutical product;

4. An identifiable reporter (source);

The fields to describe the above four criteria are as follows: -

2.6.1 Identifiable patient should have the following information:

- Patient Initials: Write first letters of name & surname e.g., Vipin Sharma should be written as VS.
- Age or date of birth: Write either the date of birth (DD/MM/YYYY) or age of the patient at the time of an Adverse Event occurred.
- Gender: Male/Female/Transgender
- Weight: In case of adult (in Kg) and in case of infant use value up to two decimals.

Note: If any of this information is missing, the ICSR will still be considered. Any one of the above can define the identifiable patient for case processing.

2.6.2 An Adverse Event

- Date of onset of adverse event
- Date of stop of adverse event
- Describe adverse event: Provide the description of the reaction in terms of nature, localization, etc. e.g patient developed erythematous maculopapular rash over upper and lower limb.

2.6.3 A suspected pharmaceutical product

1. The details of suspected medication(s) such as drug name (brand or generic), Batch No/Lot No., expiry date, marketing authorization holder, dose, route, frequency, dates of therapy started & stopped, and indication should be provided.

2. Action Taken with respect to suspect medication/medical product after adverse event:

Mention the status of action taken at the time of Adverse Event reporting as-

- **Drug withdrawn** –Was the suspect medication discontinued?
- **Dose reduced** – Was the dose of suspected medication reduced after the occurrence of Adverse Event?
- **Dose increased** – In certain situations, there may be lack of therapeutic efficacy of a medication. They are not normally reported. Medical products used in critical conditions or for life threatening diseases, vaccines, contraceptives, etc. non effectiveness is also regarded as an adverse event.
- **Dose not changed** – Was the suspected medication continued?
- **Unknown** – Where information is not known?

- **Not Applicable** – Such as case of chemotherapy, vaccination, anesthetic agents etc. (given in one dose or in cycle).

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

- **'Yes'**-If, the adverse drug reaction reappeared after re-introduction of suspected medication.
- **'No'**- If, the adverse drug reaction did not reappear after re-introduction of suspected medication.
- **'Effect unknown'-** When the above information is not available
- **Dose -** In some cases, when the suspect product is re-introduced, in those cases the dose given to the patient must be specified.

4. Concomitant drugs: The details like dose, route, frequency of all concomitant drugs should be provided in the same manner as that of suspected drugs including self-medication, Over the Counter medication, herbal medications, etc. with therapy dates.

5. Relevant tests/ laboratory data/investigation: Mention relevant laboratory tests /investigation data before & after Adverse Events.

6.Other relevant history: The relevant medical history of patient including pre-existing medical conditions (e.g., allergies, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction) and concurrent condition, if any.

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

- **Death:** If, the patient died, mention the cause and date of death.
- **Life-threatening:** If, the patient was at substantial risk of dying at the time of Adverse Events.
- **Hospitalization /prolongation of existing hospitalization:** If, Adverse Events caused hospitalization or increased the hospital stay of the patient.
- **Disability:** If, Adverse Events 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.
- **Other medically important condition:** When the event does not fit to above conditions, but the event may have put the patient at risk and required medical or surgical intervention to prevent any one of the above conditions.

8. **Outcomes:** Tick the outcome of the adverse event at the time of reporting as-
    - **Recovered/resolved:** If, the patient recovered/resolved from the adverse event.
    - **Not recovered/not resolved:** If, the patient did not recover/resolve from the adverse event.
    - **Recovering/resolving:** If, the patient is recovering/resolving from the adverse event.
    - **Fatal:** If, the patient died.
    - **Recovered/resolved with sequelae:** If, the patient has completely recovered from the adverse event (mention the date of recovery) or recovered with sequelae (e.g., scar).
    - **Unknown:** If, the outcome is not known.

2.6.4 An identifiable reporter (source);

- **Name & address:** A reporter must mention his/her name, 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 Adverse Events.
- **Reporter qualification:** Qualification of the reporter need to be mentioned.

2.7 Coding of Adverse Event

For the purpose of ICSR reporting (expedited and periodic) to National Regulatory Authority/NCC-PvPI, IPC, Marketing Authorization Holders are required to code Adverse Events, Indication preferably using latest version of MedDRA.

2.8 Reporting time lines

- All Serious Adverse Events must be reported by MAH within 15 calendar days of receipt of information from any source, to

(a) National Regulatory Authority (NRA), i.e, CDSCO through email - sae@cdsco.nic.in

(b) National Coordination Centre, Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission through email mah.nccpvpi-ipc@gov.in.

All Non-Serious Adverse Events must be reported by MAH within 30 calendar days of receipt of information from any source, to

(a) National Regulatory Authority (NRA), i.e, CDSCO through email – dci@nic.in, pharma.covig@cdsco.nic.in

(b) National Coordination Centre, Pharmacovigilance Programme of India,

Indian Pharmacopoeia Commission through email mah.nccpvpi-ipc@gov.in

Note: The adverse events due to lack of efficacy, medication error etc. must also be reported to national 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 Adverse Events.
For WHO-UMC causality assessment scale, refer Appendix -A.

2.10 Special population

2.10.1 Use of a pharmaceutical product during pregnancy or breastfeeding

Where during pregnancy, a woman has been exposed to any potential teratogenic medication, the follow up should be done till the delivery or child birth to assess the adverse outcome of maternal exposure.

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 relationship between any reported Adverse Events and the exposure to the suspected pharmaceutical product.

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

- Reports of congenital anomalies or developmental delay in foetus or child;
- Reports of fetal death and spontaneous abortion;
- Reports of serious suspected adverse reactions in the neonate.

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate reporting. This may be a condition of the

marketing authorization 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/NCC-PvPI, IPC.

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 pediatric or elderly population

The collection of safety information in pediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population.

CHAPTER-3

Preparation and Submission of Periodic Safety Update Report

Contents:

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 New Drugs & Clinical Trial Rules, 2019 there under during the post-marketing phase.

3.2 Objective

This chapter defines the recommended format, content and timelines of PSUR submission in conformity with New Drugs and Clinical Trial Rules-2019 of the Drugs and Cosmetics Act, 1940. PSURs are intended to be submitted to national regulatory authority and the MAH are also encouraged to submit the same in electronic format to NCC-PvPI, IPC 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.

1. Post marketing assessment of new drug –

(1) When a new drug is approved for marketing, assessment of safety and efficacy of the drug are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

(2) In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and

events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the drug shall be closely monitored and post marketing assessment of its benefit-risk profile shall be carried out.

(3) A person intending to import or manufacture any new drug for sale or distribution shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction report to the Central Licencing Authority emerging from the use of the drug imported or manufactured or marketed by the applicant in the country.

(4) The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.

(5) Post marketing assessment of new drug may be carried out in different ways as under: -

(A) Phase IV (Post marketing) trial- Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety and efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population. In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines. In such study, the study drug may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug free of cost, to the satisfaction of the Central Licencing Authority and the ethics committee.

(B) Post marketing surveillance study or observational or non-interventional study for active surveillance- Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licencing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert. In such studies the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new

drug are not applicable in such cases as drugs are already approved for marketing.

(C) Post marketing surveillance through periodic safety update reports- As part of post marketing surveillance of new drug the applicant shall furnish periodic safety update reports (PSURs) in accordance with the procedures as follows;

(i) The applicant shall furnish periodic safety update reports (PSURs) in order to-

a) report all relevant new information from appropriate sources;
b) relate the data to patient exposure;
c) summarise the market authorisation status in different countries and any significant variations related to safety; and
d) indicate whether changes shall be made to product information in order to optimise the use of product.

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

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the periodic safety update reports need to be submitted annually. Central Licencing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the Licencing Authority within fifteen 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 market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed. Vaccines and biologicals always considered as new drugs, unless specified, otherwise, by the Licensing Authority.

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

(v) A PSUR should be structured as follows:

(1) Title Page: The title page of periodic safety update reports should capture the name of the drug; reporting interval; permitted indication of such drug; date of permission of the drug; date of marketing of drug; licensee name and address.

(2) Introduction: This section of periodic safety update reports should capture the reporting interval; drugs intended use, mode of action, therapeutic class, dose, route of administration, formulation and a brief description of the approved indication and population.

(3) Current worldwide marketing authorisation status: This section of periodic safety update reports should capture the brief narrative over view including details of countries where the drug is currently approved along with date of first approval, date of marketing and if product was withdrawn in any of the countries with reasons thereof.

(4) Actions taken in reporting interval for safety reasons:

In case, an already approved drug is in clinical trial for any other indication/purpose in India or abroad has been reported for any safety concern, periodic safety update reports should also include actions related to safety that have been taken during the reporting interval. This data should cover any safety concern arising from investigational uses, by the sponsor of the clinical trial (s), regulatory authorities, data monitoring committees, or ethics committees, besides the date of post marketing experience.

(5) Changes to reference safety information (RSI): This section should include any significant changes in reference safety information within the reporting interval. Such changes include information relating to contraindications, warnings, precautions, adverse events, and important findings from ongoing and completed clinical trials and significant non-clinical findings, if any.

Note: Even if there is no significant change in RSI (Prescribing Information Leaflet & Company Core Data Sheet/Summary of Product Characteristics), MAHs should submit recent dated approved RSI as an Annexure.

(6) Estimated patient exposure: This section of periodic safety update reports should provide the estimates of the size and nature of the population exposed to the drug. Brief descriptions of the methods used to estimate the subject or patient exposure should be provided.

6.1 Cumulative subject exposure in clinical trial (Below points are taken from EMA guideline with permission VII.B.5.5.1).

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-B, 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-B, Table No. 02 & 03);
- ❖ 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.
- ❖ 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 SAEs 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 from India

Interval patient exposure refers as the patient exposure occurring between two data lock points of PSUR. Separate estimations should be provided for interval exposure and, when possible, cumulative exposure (since the date of marketing authorization) from India. (Refer Appendix-B, 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 exposure

An overall estimation of patient exposure should be provided. In addition, the data should be presented by indication, sex, age, dose, formulation, and region, wherever applicable. Depending upon the product, other relevant variables, such as vaccinations, etc. should be described. Whenever, there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible. Some industries may be running some programmes for ensuring patient safety such as patient support programme, if in this programme, any safety concern or serious ADR is observed, it should also be communicated to NCC-PvPI.

6.2.2 Post-approval use in special population

Where the approved drug has been used in special population, the cumulative estimated patient exposure should be provided with method of calculation.

Sources of such data may include non-interventional studies designed to obtain this information, such as registries.

The following are the examples of special population:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- 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;
- Any other vulnerable population.

6.2.3 Other post-approval use

If the MAH becomes aware of any specific pattern of use of a pharmaceutical product, which may be relevant for assessment of product safety, a brief description should be provided. Examples of such patterns of use are drug abuse

(for example, some cough syrups, anti-histamines, pregabalin, are used for sedation), misuse (such as use of antibiotics in viral infection) 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).

6.3 Cumulative and interval estimated 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-B, 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 Periodic Safety Update Reports should include the individual case information available to a licence holder and provide brief case narrative, medical history, indication treated with suspect drug, causality assessment. Provide following information:

7.1 Reference prescribing information

In this section, an updated reference prescribing information of a new drug should be provided by the MAH.

7.2 Individual cases received from India (Line listing of ICSRs)

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

7.3 Individual cases received from rest of the world

In this section an Individual cases received from rest of the world should br provided by the MAH.

7.4 Cumulative and interval summary tabulations of serious adverse events from clinical investigations.

This section of the PSUR should provide a brief narration of the serious adverse events as mentioned in the appendix…... background for the Appendix (example of Format need to be provided) 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 B, Table 8 provides cumulative tabulations of SAEs from clinical trials. While tabulating SAEs from clinical trials only those criteria should be used which are defined in NDCT Rules, 2019. This should not include non-serious adverse events.
- The causality assessment, where has been done should also be mentioned as related and not-related.
- While coding SAE (Table 8) and AE/ADR (Table 9), Preferred Term (PT) and System Organ Class (SOC) should be used.

7.5 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 drug reactions from non-interventional studies
- Solicited reports of serious ADRs

For special issues or concerns, additional tabulations of adverse drug 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-B, Table 09).

8. Studies

This section of PSURs should capture the brief summary of clinically important safety and efficacy findings obtained from the licence holder, sponsored clinical trials and published safety studies that became available during the reporting interval. 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 studies with the primary objective 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 as an Appendix. The listing should include the following information:

- Study ID (e.g., protocol number or another identifier);
- Study title;
- Study type (e.g., randomized clinical trial, cohort study, case-control study);
- Study population (including country and other relevant population descriptors, e.g., paediatric population or trial subjects with impaired renal function);
- Study initiation and completion date (as defined by the manufacturer and/or importer);
- Status: Ongoing or Completed.

8.1.1 Completed clinical study

A brief summary of clinically important safety and efficacy findings obtained from completed trial during the reporting interval should be provided. 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 study

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 engineering

and biotech products). These are referred as Advanced Therapy Medicinal Products (ATMPs).

8.1.4 Other therapeutic uses of pharmaceutical product

This should include clinically important safety information from other programmes, if and when conducted by the manufacturer and/or importer that follow a specific protocol (e.g., expanded access programmes, compassionate use programmes, particular patient uses and other organized data collection).

8.1.5 New safety data related to Fixed Dose Combination therapies

Unless otherwise specified by national regulatory authority requirements, the following 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 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 a 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 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 scientific literature or made available as unpublished data, 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 as wide as possible and 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 or without 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 findings

9. **Other Information:** This section of PSURs should include the details about signal and Risk Management Plan in place by licence holder (if any). (For detail please refer Module 6)

(a) Signal and risk evaluation: In this section, licence holder will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.

(b) Risk management plan: In this section, licence holder will provide the brief details of safety concern and necessary action taken by him to mitigate these safety concerns.

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 within 15 days after the data lock point of the PSUR 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 increase in liver enzymes 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-C, 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 safety concern (not considered a signal) be monitored and reported in a PSUR, the MAH should summarize the result of the analysis of such safety concern in this section even if it is negative.

10. **Overall Safety Evaluation:** This section of PSURs should capture the overall safety evaluation of the drug based upon its risk benefit evaluation for approved indication.

The purpose of this section is to provide:

- Important identified risks;
- Important potential risks;
- Important missing information.
- In case a signal was indicated in previous interval report and now has been refuted because of new evidences which resulted in closure, should be specifically mentioned here.
- 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 (if any) 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.

10.2 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

Wherever necessary, 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.

New information about efficacy/effectiveness in uses other than the approved indication(s) (off-label use) 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 a clear information about the benefit 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 provided. This sub-section should

provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, as follows:

- 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 challenge the validity of a surrogate endpoint, if used
- Clinical relevance of the effect size
- Generalizability 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 generalizable 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 is 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 included 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 described.

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

- The assumptions, considerations, and judgement or weighing 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. Conclusion:

This section of PSURs should provide the details on the safety profile of drug(s) and necessary action taken by the license holder in this regard.

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 national regulatory authority. This may include proposals for additional risk minimization activities. These proposals should also be considered for incorporation into the Risk Management Plan.

12. **Appendix**: The appendix includes the copy of marketing authorization in India, copy of prescribing information, line listings with narrative of Individual Case Safety Reports.

CHAPTER 4

Quality Management System at Marketing Authorization Holder Organization

Contents:

4.1 Introduction

4.2 Scope

4.3 Structures and Processes

4.4 Specific quality system procedures and processes

4.1 Introduction

This module contains guidance for the Marketing Authorization Holders for the establishment, maintenance, performance, performance and quality assurance of PV system.

4.2 Scope

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

4.3 Structures and Processes

4.3.1 Pharmacovigilance system

All MAH should have the PV system which should comply with the quality management system including requirements of NDCT Rules 2019, Schedule M of the Drugs & Cosmetics Act, 1940, and Rules thereunder.

The PV system at MAH should have an organogram describing PV personnel's roles and responsibilities, procedures, processes and resources, including management of resources, compliance and records (Refer Chapter 1 for more details).

4.3.2 Quality Management System (QMS) of PV

The QMS in PV is a framework of policies, procedures and system necessary to ensure quality related to detection, assessment, understanding, evaluation and prevention of adverse events on pharmaceutical products.

The quality management system is based on the following activities:

- Quality planning: Establishing structures of PV system, planning, effective integration and consistent processes for safety;
- Quality adherence: Carrying out tasks and responsibilities in accordance with quality requirements such as collection of ICSRs, completeness of report, case narrative, data management, causality assessment, signal management, etc.;
- Quality control and assurance: By monitoring the parameters described under quality adherence;
- Quality improvements: Taking Corrective and Preventive measures, as and when required, to ensure patient safety.

4.3.3 Requirements and Responsibilities of QMS at MAH site

MAH should have a sufficient number of competent and appropriately qualified, and trained personnel for the performance of PV activities.

In case, where MAH has completely outsourced the PV activities, through a valid contract, the outsourced agency/institution should comply with the above statement. The responsibility of adhering to PV QMS will ultimately lie with MAH.

The managerial staff in the organization should be responsible for compliance of PV Guidance Document for MAHs of Pharmaceutical Products.

4.3.4 Training of MAH personnel for PV

The personnel involved in PV activities should receive induction (within one month of joining and continued trainings with proper evaluation of performance, thereafter. The organization should maintain the training plans and records of trainings. The organization should keep identifying the continued training needs.

4.3.5 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, identified, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for PV System.

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, MAHs should 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 Chapter 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 Chapters 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 Chapters 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 Chapters 2, 3 and 6 for detailed information)

•Effective communication with regulatory authority, including communication on new or changed risks, the PVMF (refer Chapter 1 for detailed information), risk management systems (refer Chapter 6 for detailed Information), PSURs (refer Chapter 3 for detailed information) and CAPAs (refer Chapters l & 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 electronic copies of the PV records should be stored indefinitely. Time line to store hard copies need to be confirmed with CDSCO.

4.4.3 Documentation of the quality system

All elements, requirements and provisions adopted for the quality system should 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 Chapter 1 for detailed information).

4.4.4 Critical PV processes

The following PV processes should be considered as critical:

- Benefit-risk evaluation;
- Establishing, assessing & 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;
- 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.
- 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 the effectiveness of QMS in PV

The QMS in PV should be continuously monitored for its effectiveness by the MAH through the following processes:

- System reviews 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 Chapter 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 PVOIC for PV

Refer Chapter 1 for detailed information.

CHAPTER 5

Audit & Inspection of Pharmacovigilance System at Marketing Authorization Holder Organization

Contents:

5.1 Introduction

This chapter provides insights into planning, conducting, reporting and follow-up of PV inspections by regulatory authorities/officials responsible for inspection.

5.2 Objectives

The objectives of PV audits and inspections are as below:

- To verify by examination and evidence, the appropriateness of the implementation and operation of the PV system including its quality systems.
- 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/audits.

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

5.3 Inspection Types

The Inspections of PV can be routine or targeted to MAHs suspected of being non-compliant.

5.3.1 Routine inspection

These inspections are planned and informed inspection of the PV system of MAH. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet the regulatory PV obligations for the marketed pharmaceutical products in India.

These inspections are prioritized on the risk-based approach.

5.3.2 Targeted inspections

These inspections are 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 are as below (but not limited to):

- Continuous delays or omission and poor-quality reporting of I CSRs/PSURs/RMPs.
- Failure to provide the asked information or data within the deadline specified by regulatory authority.
- Delays or failure to carry out specific obligations related 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 pharmaceutical product withdrawal and recall.

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 carried out.

The PV inspection team will be made by CDSCO including representative(s) from PvPI.

The inspection will be planned based on the following:

- Compliance history identified during previous PV inspections.
- Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection
- MAH with sub-contracted PV activities (qualified person responsible for PV functions in India, reporting of safety data, etc.) and 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 PSMF management.
- Change of PVOIC 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.

Chapter 6

Submission of Risk Management Plan

Contents:

6.1 Introduction

6.2 Objectives

6.3 Contents of RMP

6.1 Introduction

At the time of marketing authorization, information on the safety of a pharmaceutical product is relatively limited as the clinical studies are carried out in aa relatively small number of subjects, restricted population in terms of age, gender, ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up.

A pharmaceutical product is authorized on the basis that at the time of authorization, the benefit-risk balance is positive. The product may have multiple risks of varying degree associated with it and individual risks will vary from product to product. All actual or potential risks might not have been identified at the time of initial authorization. Many risks will only be discovered and characterised during post-marketing phase.

The aim of Risk Management Plan (RMP) is to document the risk management system considered necessary to identify, characterise and minimise a pharmaceutical product's important risks. The Risk Minimization strategy involves continuous monitoring of efficacy and safety profile-Risk Identification, Risk Assessment, Risk Characterization, Risk Communication and Risk Mitigation.

Objectives

- Identification and characterization of risk to update the safety profile of the pharmaceutical product(s);
- Indicate how to characterize further the safety profile of the pharmaceutical product(s);

- Document measures to prevent or minimize the risks associated with a pharmaceutical product, including an assessment of the effectiveness of interventions;
- Document post-marketing obligations that have been imposed as a condition of the marketing authorization;
- Document any change in the risk profile of a pharmaceutical product(s) after marketing authorization.

The RMP document is a dynamic, stand-alone document which should be updated throughout the life-cycle of a pharmaceutical products.

The Licence holder will provide the details of safety concern and necessary action taken by him to mitigate any safety concern in the applications of PSUR.

6.2 Description of RMP

6.2.1 Pharmaceutical product overview

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

- Active Pharmaceutical Ingredient(s) information, name of MAH, date and country of first launch/authorization worldwide (if applicable), chemical class, indication (s), mechanism of action, route of administration, pharmaceutical form and strength.
- Information on the excipients used in the formulation of a pharmaceutical product should be provided.
- Administrative information on the RMP such as data lock point, date submitted and version number of all parts of RMP.

6.2.2 Safety specifications

The MAH should provide a synopsis of the safety profile of a pharmaceutical product(s) and should include, what is known and unknown about the pharmaceutical product(s) safety. The safety specification consists of following subsections:

6.2.2.1 Epidemiology, 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.

6.2.2.2 Non-clinical part of the safety specifications:

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

6.2.2.3 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-paediatric, geriatric etc.) and also by the type of clinical trial.

6.2.2.4 Populations not studied in clinical trials:

This section describes, 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 exclusion criteria such as paediatric population, geriatrics population, pregnant/lactating women, hepatic /renal impairment patients etc.

6.2.2.5 Post-marketing experience:

This section should provide information on the number of patients exposed during post-marketing phase; how the pharmaceutical product has been used in clinical practice, 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.

6.2.2.6 Identified and potential risks:

This section provides information on the important identified and potential risks associated with the use of a pharmaceutical product and potential Adverse Events/Adverse Reactions with other pharmaceutical products, foods, 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.

6.2.2.7 Summary of the safety concerns:

At the end of the RMP document, summary of the "Safety concerns/measures" of pharmaceutical products should be provided.

6.2.3 PV activities

MAH should list the various PV activities involved to identify a new safety concern or further characterize known safety concerns or investigation of potential safety concerns, whether it is real or not and 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 carried out against the safety concern.

6.2.4 Risk minimization activities

The MAH should have the updated Package inserts, Product labelling, Product Information Leaflet (PIL), pack size, risk minimization activities. The MAH should also consider when appropriate to have additional Risk minimization activities like educational material, communication letter to Healthcare Professionals (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,
- 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**
2. **New Drugs and Clinical Trials Rules 2019**
3. **PvPI Guidance for Spontaneous reporting Document**
4. **Guidance for Industry on Pharmacovigilance Requirements for Biological Products-CDSCO**
5. **ICH Guideline: E2E: Pharmacovigilance Planning**
6. **ICH-E2C (R2): Periodic Benefit-Risk Evaluation Report**
7. **ICH-E2D: Post-Approval Safety Data Management: Definition in Standards for Expedited Reporting**
8. **ICH-E3: Structure and Content of Clinical Study Report**
9. **Good Pharmacovigilance Practices (GVP) of European Union**
10. **WHO- UMC: Global Pharmacovigilance**

Appendices:

Appendix A:

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 recognized 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

Appendix B:

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	2 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	2 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 (which ever applicable)				
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others	EU	Japan	Mexico	US/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 (which ever applicable)				
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intraveno	Oral	Others	EU	Japan	Mexico	US/Canad	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		Active Comparator		Placebo	Causality Assessment (Related (R) and Not related (NR)
Preferred Term	**Listed**	**Not Listed**	**Listed**	**Not Listed**		
Blood and lymphatic system disorders						
Anemia						
Bone Marrow Necrosis						
Cardiac						

disorders						
Tachycardia						
Ischemic cardiomyopathy						

Table 09: Number of ADRs using the term (System Organ Class (SOC) and preferred term (PT) from Post-Marketing Sources

	Report Sources (Literature, Spontaneous, solicited or any other)					**Non-interventional post-marketing sources**	
	Serious		**Non-serious**		**Total Spontaneous**	**Serious**	
	Interval	**Cumulative**	**Interval**	**Cumulative**		**Interval**	**Cumulative**
SOC 1							
PT							
SOC 2							
PT							

Appendix C:

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/YYY	Ongoing	MM/YYY	Meta analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MM/YYY	Closed	MM/YYY	Spontaneous case reports & one case report in Phase IV	Rash already an identified risk SJS not reported in pre	Targeted follow up of reports with site visit to one hospital.	RSI updated with a Warning and Precaution

				trial	authorization CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset	Full review of cases by manufacturer and/or importer dermatologist and literature searches	DHPC sent to oncologists 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 D:

PSUR Summary Report Checklist

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

S. No.	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 (e.g. New safety information)		
4.	**Status in India**			
4.1	Marketed (since)			
4.2	Non-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.	**Appendices (indicate if included in the submission)**			
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 E:

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 dis ease, 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 favorable (beneficial) and unfavorable 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 in format ion, 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 New Drugs and Clinical Trials rule 2019- "new drug" means,— (i) a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or (ii) a drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or (iii) a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or (iv) a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or (i) a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or

	xenografts, intended to be used as drug; Explanation.— The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;
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.