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Pharmacovigilance Guidance Document

for

Marketing Authorization Holders of Pharmaceutical Products

Published by:

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

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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 Cosmetics Act, 1940 & Rules, 1945 or any other relevant Act and are subject to being in conformity with the Drugs and Cosmetics 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 Cosmetics Act, 1940 & Rules, 1945. This document will help in bringing 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 organization, Audits and Inspection of Pharmacovigilance System at MAH organization 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 (MAH refers to manufacturer, marketer or the importer of the drug, who has valid manufacturing, marketing or import licence 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 organization, Audits and Inspection of Pharmacovigilance System at MAH organization 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 organization. This guidance document may be amended from time to time after obtaining necessary approvals from the concerned authorities. To publish the Pharmacovigilance Guidance Document for MAHs of Pharmaceutical Products, Version 2.0, Expert Committee was constituted. The Committee consisted of:

Chairperson : Prof. Y.K Gupta, President, AIIMS-Bhopal

Members:

- Dr Rubina Bose, Dr Swati Srivastava & Dr I. S. Hura, Deputy Drugs Controller (India), CDSCO.
- Dr Kiran Marthak, Representative, Indian Drug Manufacturers Association (IDMA).
- Dr T. V. Narayana, National President, Indian Pharmaceutical Association (IPA).

Member Secretary

- Dr Jai Prakash, Officer-in-Charge of PvPI, IPC

Acknowledgements

The National Coordination Centre for Pharmacovigilance Programme of India (PvPI) acknowledges the efforts of the Expert Committee for thoroughly going through the content of this Pharmacovigilance Guidance Document for Marketing Authorization Holders (MAHs) of Pharmaceutical Products and giving their critical inputs in the revision process. The comments/suggestions obtained from the following organization are also gratefully acknowledged;

- Alkem Laboratories Limited
- Bayer Pharmaceuticals Private Limited
- Emcure Pharmaceuticals Limited
- FDC Limited
- Glenmark Pharmaceuticals Limited
- Indian Society for Clinical Research (ISCR) PV Council
- IPCA Laboratories
- IQVIA
- Mylan Viatris Pharmaceuticals Limited
- Ovia MedSafe Private Limited
- Product Life Group
- Reliance Life Sciences Private Limited
- Serum Institute of India Limited
- Sun Pharma Industries Limited
- Venus Remedies Limited
- Win Medicare Private Limited
- Zydus Lifesciences Limited

The NCC-PvPI, IPC also acknowledges the comments offered by the following special invitees;

- Dr B. K. Rana, CEO, Quality & Accreditation Institute (QAI), Noida, U.P.
- Dr Manoj Sharma, Assistant General Manager & QPPV -Global Pharmacovigilance Department, Win-Medicare Private Limited, New Delhi.
- Dr Mita Nandy, Medical Expert, Noida, Uttar Pradesh.
- Dr Satyajit Mohapatra, Director, SRM Centre for Clinical Trials and Research, Chennai, Tamil Nadu.
- Professor Suparna Chatterjee, Department of Pharmacology, IPGMER, Kolkata.
- Dr Vivek Ahuja, Sr. Vice President, Delivery Excellence, Strategy and Growth, PV, Quality and Regulatory Services, EVERSANA.
- Dr Deepak Polpakara, Senior Team Lead, AEFI Secretariat, New Delhi.

The NCC-PvPI, IPC appreciates the following NCC-PvPI, IPC staff for their valuable support to revise this PV Guidance Document for MAHs of Pharmaceutical Products:

- Dr Jai Prakash, Officer-in-Charge, PvPI, IPC, Ghaziabad.
- Dr Shashi Bhushan, Sr. Scientific Officer, PvPI, IPC, Ghaziabad.
- Dr R. S. Ray, Scientific Assistant, PvPI, IPC, Ghaziabad
- Mr. Vipin Sharma, Team Lead, Signal Division, PvPI, IPC, Ghaziabad
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- Ms Deepti Sachdeva, Ex-Pharmacovigilance Associate, PvPI, IPC, Ghaziabad
- Ms Priyanka Sharma, Graphic Designer, PvPI, IPC, Ghaziabad

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Secretary-cum-Scientific Director
Indian Pharmacopoeia Commission
Ghaziabad-201002 &
Drugs Controller General of India
Central Drugs Standard Control Organization
FDA Bhawan, New Delhi-110002

Process of Preparation of Pharmacovigilance Guidance Document for MAHs of Pharmaceutical Products

An Expert Committee was constituted to revise the existing PV Guidance Document for MAHs of Pharmaceutical Products, Version 1.0

↓

PV Guidance document, Version 1.0 reviewed by organising 10 Expert Committee meetings and incorporated their comments.

↓

Public/stakeholders comments obtained by uploading the draft version 2.0 of PV Guidance Document for MAHs of Pharmaceutical Products on website of IPC www.ipc.gov.in for 30 days

↓

Examination of comments/suggestions obtained by the Expert Committee

↓

Incorporation of valid comments by the NCC-PvPI Team at IPC

↓

The pre-print version circulated to the Expert Committee for review and approval

↓

Final version approved by the Competent Authority and printed

What is new in this document ?

- This guidance document is updated in the light of New Drugs and Clinical Trials Rules, 2019 and revised Schedule M of Drugs and Cosmetics Rules, 1945.
- The terminology for PVOI is replaced with PVOIC.
- The "Module" is replaced with "Chapter"
- Definition of New Drug is updated in accordance with NDCT Rules, 2019
- The Marketing Authorization Holders should maintain records in Excel/Electronic sheets.
- All Non-Serious Adverse Events should be reported by MAHs within 90 calendar days.
- The International Classification of Diseases (ICD) is replaced with MedDRA dictionary for coding of "Indication" during entry of Individual Case Safety Reports (ICSRs).

- Appendix A – Simplified E2B Guide for Primary Reporters document id 01-15-006, Version 1.1 by WHO-UMC removed from this Guidance Document.
- In Appendix E – PSUR Summary Report Checklist which was existing in previous version of this document has been removed
- Frequently Asked Questions (FAQs) incorporated in Appendix E.

CONTENTS

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AIIMS	All India Institute of Medical Sciences
AMC	Adverse Drug Reaction Monitoring Centre
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
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
MoHFW	Ministry of Health & Family Welfare

ABBREVIATIONS

MedDRA	Medical Dictionary for Regulatory Activities
NCC	National Coordination Centre
NDCT Rules 2019	New Drug and Clinical Trial Rules, 2019
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
UMC	Uppsala Monitoring Centre
UT	Union Territory
WHO	World Health Organization
XML	Extensible Markup Language

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 (MoHFW), 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 and implement 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 is defined as the 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, marketer or the importer of the drug, who has valid manufacturing, marketing 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, new products should be monitored for a specific period and 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 and 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 a 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, blood & blood related products and veterinary products.

Objectives

The Pharmacovigilance Guidance Document for MAHs of Pharmaceutical Products 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 organization across the country by:
   (i) Preparation and maintenance of Pharmacovigilance System Master File
   (ii) Collecting, Processing and Reporting of Individual Case Safety Report (ICSR) by Marketing Authorization Holder (MAH)
   (iii) Preparation & Submission of Periodic Safety Update Report by MAH
   (iv) Implementation of Quality Management System at MAH organization
   (v) Audits & Inspections of Pharmacovigilance System at MAH organization
   (vi) Preparation and Submission of Risk Management Plan

Scope

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

(i) Drugs, New Drugs, subsequently approved drugs including Fixed Dose Combination(s) etc.
(ii) Biologics including Biosimilars, Cell lines/culture-based products etc.
(iii) Radiopharmaceuticals
(iv) Phytopharmaceuticals Products

Note: For vaccines, Refer

(a) Guidance for industry on PV Requirements for Biological Products by CDSCO.
(b) Adverse Event following Immunization (AEFI) Surveillance & Response Operational Guidelines-2024

Roles & Responsibilities of Different Authorities

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

a) Central Drugs Standard Control Organization (CDSCO)

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 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 there 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.

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 annually for subsequent two years. 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.

b) 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 Authority. The State Drugs Controllers are primarily responsible for licensing of manufacturing and sale/distribution of drugs.

As per the requirements under Section 6.11 of Schedule M (Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products) of Drugs Rules 1945 as amended vide Gazette Notification No. 922(E), dated 28th December, 2023 mentions that "The licensee shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the adverse drug reactions emerging from the use of drugs manufactured or marketed by the licensee". Therefore, MAHs should submit the ADRs with the use of drugs manufactured or marketed by them to the licensing authority. The MAHs are also encouraged to report all Adverse Events to the NCC-PvPI, IPC.

c) 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 medicines outweigh the risks associated with its use. The All India Institute of Medical Sciences (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 World Health Organization-Programme for International Drug Monitoring by contributing ADRs to Uppsala Monitoring Centre (UMC), Sweden. The 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 Adverse Drug Reaction Monitoring Centers (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 AE in Hindi, English and other vernacular languages, mobile app,

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 Vector-Borne Diseases Control Programme (NCVBDCP) etc.

There are following expert's panels/committees/group 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 also help promote and protect public health.

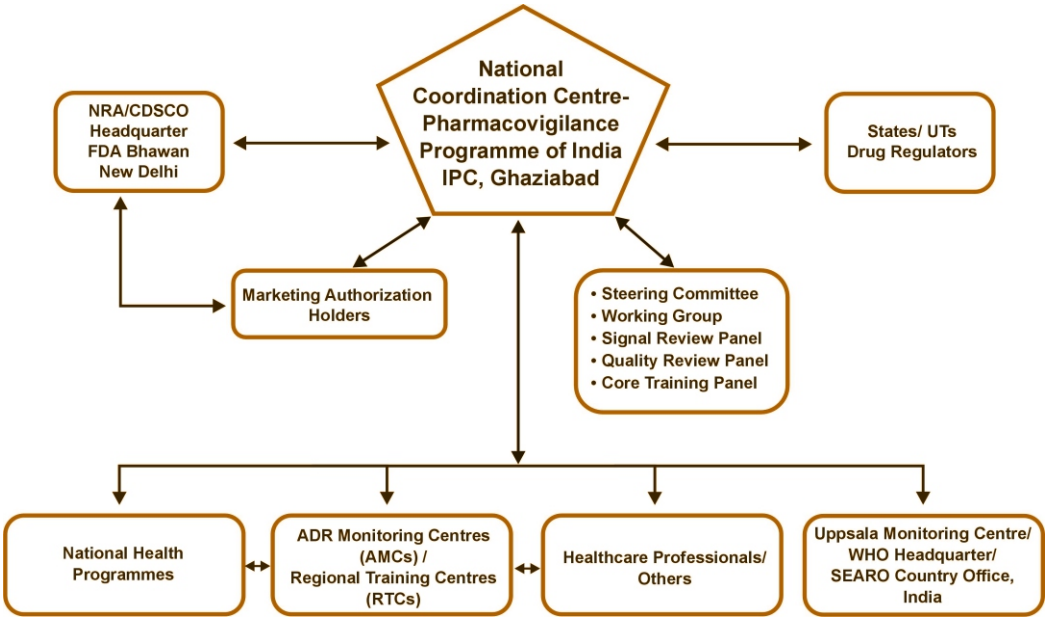

Figure I: PvPI-Communication Network

CHAPTERS

Chapter-1

Pharmacovigilance System Master File (PSMF)

Contents

1 Pharmacovigilance System Master File (PSMF)

1.0 Introduction

The Pharmacovigilance System Master File (PSMF) provides a description of the pharmacovigilance system used by the MAHs 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.

1.1 Scope

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

1.2 Contents of the PSMF

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

1.2.1 Pharmacovigilance personnel and their responsibilities: -

Pharmacovigilance Officer-in-Charge (PVOIC): 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. Where the PVOIC is a pharmacy professional, there should be a back-up of medically qualified person for causality assessment, as and when required. The PVOIC shall be responsible for the following:

(i) Development of training modules and organizing training for staff of PV department;

(ii) Identification of PV activities and framing of SOPs, revision of SOPs;

(iii) Establishment and maintenance of Quality Management System (QMS) of PV department;

(iv) 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:

(a) Contact details (Name, address, phone, e-mail)

(b) Summary, curriculum vitae with the key information on the role of the PVOIC

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

(d) Details of Deputy PVOIC; A deputy PVOIC will work in the absence of PVOIC. He/she will discharge all role and responsibilities of PVOI

The qualification of deputy PVOIC will be same as that of PVOIC as mentioned above.

1.2.2 Pharmacovigilance Organization Structure

1.2.2.1 Marketing Authorization Holder

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

1.2.2.2 Contract Research Organization (CRO)

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 CRO & operational units relevant to the fulfilment of PV obligations should be provided. It should include:

(i) The PV organizational structure of the CRO showing the organogram of the PV department

(ii) Name & address of the organization, where the PV functions are undertaken such as collection of AEs, ICSRs processing, preparation & submission of PSURs, signal detection, RMP, post-marketing surveillance and management of safety variations

(iii) Delegated activities (contracts and agreements)

(iv) Service providing system (e.g., medical information, auditors, patient support programme providers, study data management etc.)

(v) Commercial arrangements (distributors, licensing partners, co-marketing etc.)

(vi) Technical providers (hosting of computer systems and their validation etc.)

1.2.3 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 from all sources. The main sources for safety data will be as follows:

(i) Medical information inquiries

(ii) "Contact us" emails, website inquiry forms and helpline etc.

(iii) Pharmaceutical product market complaints-Receipt, handling and disposal

(iv) MAH employees involved in PV activities

(v) Spontaneous information from patient or their care givers and follow up of information

(vi) Published literature

(vii) Spontaneous reporting by Healthcare Professionals (HCPs)

(viii) Reports from internet, digital media or social media

(ix) Patient-support programmes

(x) Reports from National Regulatory Authority

(xi) Contract partners involved in PV activities

(xii) Market Research Programmes

1.2.4 Pharmacovigilance Processes

1.2.4.1 Description

(i) 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

(ii) The procedures for collection, collation, processing, assessment, reporting and follow-up of ICSR

(iii) Compilation of ICSR for the submission of PSURs

(iv) Review of ICSR, signal detection (if any), Drug Safety Alerts, Corrective and Preventive Action (CAPA)

(v) Communication of Drug safety concerns to Consumer, HCPs, PvPI and the National Regulatory Authority

(vi) Summary of Product Characteristics (SmPCs) and Prescribing Information Leaflets (PILs) with history of revisions

1.2.4.2 SOPs should include the following:

(i) Description of the process, data handling and records of PV performance

(ii) ICSR collection, collation, follow-up, causality assessment and reporting;

(iii) PSUR scheduling, preparation and submission

(iv) Quality issue, recall or withdrawal of pharmaceutical products

(v) Training procedures, evaluations and documentations

(vi) Signal detection and evaluation process

(vii) Communication of safety concerns to consumers, HCPs and regulatory authorities

(viii) Implementation of safety variations in PILs/SmPCs

(ix) Safety data exchange agreements, if any

(x) Safety data archival and retrieval

(xi) PV audit and inspections

(xii) Quality control for PV activities

(xiii) Risk Management Plan

(xiv) Any other relevant SOP for establishing PV system at MAH organization

1.2.4.3 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.

1.2.4.4 Quality Management System (QMS) in Pharmacovigilance

The QMS should be established in PV activities, which should include:

(i) 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/excel spreadsheet/electronic data management tools for recording primary information received for every adverse event reported.

(ii) Trainings : A summary of training 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 products safety reports.

(iii) Auditing : The Quality Assurance (QA) of the organization should supervise/facilitate the internal and 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).

1.2.5 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:

(i) 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

(ii) 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

(iii) An overview of the timelines of PSUR reporting

(iv) An overview of the methods used to ensure submission of safety variation to competent authority

(v) Wherever applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to PV

1.3 Annexures to the PSMF

(i) A list of pharmaceutical products including the name of the pharmaceutical product, active substance(s) and excipients

(ii) A list of contract agreements covering delegated activities including the pharmaceutical products

(iii) A list of tasks delegated by the PVOIC for PV

(iv) A list of all completed audits/inspection (regulatory as well as internal) and a list of audit/ inspection schedules

Chapter-2

Collection, Collation, Processing & Reporting of Individual Case Safety Reports (ICSRs)

Contents

2 Collection, Collation, Processing & Reporting of Individual Case Safety Reports (ICSRs)

2.0 Introduction

This chapter highlights the general principles for the collection, collation, processing & reporting of Individual Case Safety Reports associated with pharmaceutical products marketed in India for human use.

2.1 Structure & Processes

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

2.1.1 Collection and Collation of ICSR

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

2.1.1.1 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.

2.1.1.2 "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.

2.1.1.3 MAH's employees designated for the PV work

The employees of the MAH designated for the PV work, should be periodically trained on applicable regulations, SOPs and their assigned responsibilities. All other employees should be periodically made aware of the importance of reporting of Adverse Events to the PV department, if and when come to their knowledge.

2.1.1.4 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.

2.1.1.5 Information on Adverse Events from the internet or digital media

The MAHs should regularly screen relevant websites or digital media (including newspapers etc.) or social media under their management or responsibility for potential reports of AEs. 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. The MAHs may also consider utilizing their websites/portals to facilitate the collection of AEs.

2.1.1.6 Solicited reports

As defined in ICH-E2D, solicited reports of suspected AEs 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 AEs obtained from any of these data collection systems should not be considered spontaneous.

2.1.1.7 Miscellaneous sources for reporting

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

2.2 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. The MAHs should perform at least weekly literature review of their pharmaceutical products by using electronic literature data base (such as PubMed, Science Direct, Scopus, AdisInsight etc.). Any AE identified by this

process need to be processed as per spontaneous ICSR. The MAHs are advised to submit ICSR to CDSCO/NCC-PvPI along with the complete literature reference including Digital Object Identifier (DOI) or copy of full-length article, wherever feasible.

2.3 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 2.5, reporting of ICSR) required for clinical evaluation of the ICSR.

Follow up attempt(s) should be made to seek the details of any missing information/clinical evaluation of ICSR. The procedure of follow up shall be documented and shall be preferably closed within one month. While reporting to PvPI/CDSCO, the MAH should clearly indicate that the reported ICSR is either initial or follow up.

2.4 Processing of ICSR

2.4.1 ICSR receipt

2.4.1.1 Date of receipt

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

2.4.1.2 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.

2.5 Reporting of ICSR

Only valid ICSR (as stated below) would qualify for reporting to NCC-PvPI & National Regulatory Authority. The ICSR should be reported in current version of E2B XML format to NCC-PvPI, IPC.

The valid ICSR would be one, which meets the following minimum criteria for reporting:

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

(i) An Adverse Event

(iii) A suspected pharmaceutical product

(iv) An identifiable reporter (source)

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

2.5.1 Identifiable patient should have the following information:

2.5.1.1 Patient Initials: Write first letter of name & surname e.g., Vipin Sharma should be written as VS.

2.5.1.2 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.

2.5.1.3 Gender: Male/Female/Transgender

2.5.1.4 Weight: In case of adult (in Kg) and in case of infant use value up to two decimals.

2.5.2 An Adverse Event

2.5.2.1 Date of onset of adverse event

2.5.2.2 Date of stop of adverse event

2.5.2.3 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.

2.5.3 A suspected pharmaceutical product

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

2.5.3.2 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 (De-challenge) – Discontinuation of suspect medication after Adverse Event.

(i) Positive de-challenge - If, the Adverse Drug Reaction recovered after withdrawal of suspected medication.

(ii) Negative de-challenge - If, the Adverse Drug Reaction did not recover after withdrawal of suspected medication.

(iii) Dose reduced – Was the dose of suspected medication reduced after the occurrence of Adverse Event?

(iv) **Dose increased** – Was the dose of suspected medication increased after the occurrence of Adverse Event?

(v) **Dose not changed** – Was the suspected medication continued?

(vi) **Unknown** – Where information is not known?

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

Re-challenge details: Mention the status on Re-challenge as-

(i) **Rechallenge:** Re-administration of same suspected medication at same dose.

(ii) **Positive re-challenge:** If, the adverse drug reaction reappeared after re-introduction of suspected medication.

(iii) **Negative re-challenge:** If, the adverse drug reaction did not reappear after re-introduction of suspected medication.

(iv) **Effect unknown:** When the above information is not available

Note : In some cases, when the suspect product is re-introduced, in those cases the dose given to the patient must be specified.

2.5.3.3 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.

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

2.5.3.5 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.

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

(i) **Death:** If, the patient died, mention the cause and date of death.

(ii) **Life-threatening:** If, the patient was at substantial risk of dying at the time of Adverse Events.

(iii) **Hospitalization /prolongation of existing hospitalization:** If Adverse Events caused hospitalization or increased the hospital stay of the patient.

(iv) **Disability:** If Adverse Events resulted in a substantial disruption of a person's ability to conduct normal life functions.

(v) **Congenital anomaly:** If exposure of the drug prior to conception or during pregnancy may have resulted in a birth defect.

(vi) **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.

2.5.3.7 Outcomes: Appropriately tick the outcome of the Adverse Event at the time of reporting as

(i) **Recovered/resolved:** If, the patient recovered/resolved from the adverse event.

(ii) **Not recovered/not resolved:** If, the patient did not recover/resolve from the Adverse Event.

(iii) **Recovering/resolving:** If, the patient is recovering/resolving from the Adverse Event.

(iv) **Fatal:** If the patient died.

(v) **Recovered/resolved with sequelae:** If, the patient has completely recovered from the adverse event (mention the date of recovery) with sequelae (e.g., scar).

(vi) **Unknown:** If, the outcome is not known.

2.5.4 An identifiable reporter (source)

2.5.4.1 Name & address: A reporter must mention his/her name, address and contact details. The identity of the reporter will be maintained confidential.

2.5.4.2 Date of report: Mention the date on which he/she reported the Adverse Events.

2.5.4.3 Reporter qualification: Qualification of the reporter needs to be mentioned.

2.6 Coding of Adverse Event & Indication

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

2.7 Reporting time lines

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

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

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

2.7.2 All Non-Serious Adverse Events must be reported by MAH within 90 calendar days of receipt of information from any source, to

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

(ii) 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 NCC-PvPI, IPC/National Regulatory Authority.

2.8 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.

2.9 Special population

2.9.1 Use of a pharmaceutical product during pregnancy or breast feeding

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:

(i) Reports of congenital anomalies or developmental delay in fetus or child;

(ii) Reports of fetal death and spontaneous abortion;

(iii) 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.*

2.9.2 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 (PSUR)

Contents

3 Preparation and Submission of Periodic Safety Update Report

3.0 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 thereunder during the post-marketing phase.

3.1 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 NRA online through the SUGAM portal at www.cdscoonline.gov.in 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 for the approved indications. The PSUR, is therefore, a tool for post-marketing evaluation at defined time points in the life cycle of a pharmaceutical product.

3.2 Post marketing assessment of new drug

3.2.1 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.

3.2.2 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.

3.2.3 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.

3.2.4 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.

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

3.2.5.1 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.

3.2.5.2 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 the 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.

3.2.5.3 Post marketing surveillance through Periodic Safety Update Reports - As part of post marketing surveillance of a 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 marketing 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 Report. Within the single Periodic Safety Update Report 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 the subsequent two years – the Periodic Safety Update Reports need to be submitted annually. The 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 Report(s) 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 events must be reported to the Licencing Authority within fifteen Calendar days of initial receipt of the information by the applicant. If the marketing of a new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on a deferred basis beginning from the time of the new drug is marketed. Vaccines and biologicals are 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 Report.

3.3 Structure of PSUR : The PSUR should be structured as under:-

3.3.1 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.

3.3.2 Introduction: This section of Periodic Safety Update Report 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.

3.3.3 Current worldwide marketing authorisation status: This section of Periodic Safety Update Report should capture the brief narrative over view including details of countries where the drug is currently approved along with the date of first approval, date of marketing and if the product was withdrawn in any of the countries with reasons thereof.

3.3.4 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 e.g. Drug Alerts published by USFDA/EMEA or other regulatory agencies, 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.

3.3.5 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 latest dated approved RSI as an Annexure.

3.3.6 Estimated patient exposure: This section of Periodic Safety Update Report 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 on:

3.3.6.1 Cumulative and interval subject exposure in clinical trial:

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

(i) 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 1)**.

(ii) 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. 2 & 3)**.

(iii) 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.

(iv) 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.

(v) 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).

(vi) 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.

(vii) 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.

(viii) For individual trials of particular importance, demographic characteristics should be provided separately, if available.

3.3.6.2 Cumulative and interval patient exposure from Marketing Experience in 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. 4 and 5)**. 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:

(i) 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 CDSCO and NCC-PvPI, IPC.

(ii) 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:

a) Pediatric population

b) Elderly population

c) Pregnant or lactating women

d) Patients with hepatic and/or renal impairment

e) Patients with other relevant co-morbidity

f) Patients with disease severity different from that studied in clinical trials

g) Sub-population carrying relevant genetic polymorphism(s)

h) Patients of different racial and/or ethnic origin

i) Any other vulnerable population

(iii) 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 etc. 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).

3.3.6.3 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 6 and 7)**. The data should be presented as mentioned in the **section 6.2**.

3.4 Presentation of individual case histories

This section of Periodic Safety Update Report should include the individual case information available to a license holder and provide brief case narrative, medical history, indication treated with suspect drug and causality assessment. Provide following information:

3.4.1 Reference prescribing information

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

3.4.2 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.

3.4.3 Individual cases received from rest of the world

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

3.4.4 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 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.

(i) **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 the NDCT Rules, 2019. This should not include non-serious adverse events.

(ii) The causality assessment, where has been done should also be mentioned as related and not-related.

(iii) While coding SAEs **(Table 8)** and AEs/ADRs **(Table 9)**, Preferred Term (PT) and System Organ Class (SOC) should be used.

3.4.5 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 AEs/ADRs from the date of marketing authorization to the data lock point of the current PSUR.

The tabulation should include:

(i) Serious and non-serious AEs/ADRs from spontaneous ICSR, including reports from HCPs, consumers, scientific literature, and regulatory authorities

(ii) Serious ADRs from non-interventional studies

(iii) Solicited reports of serious AEs/ADRs

For special issues or concerns, additional tabulations of ADRs 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 9)**.

3.5 Studies

This section of periodic safety update reports should capture the brief summary of clinically important emerging efficacy or effectiveness and safety findings obtained from the licence holder, sponsored clinical trials and published safety studies that became available during the reporting interval of the report which has potential impact on product safety information.

3.5.1 Summaries of significant safety findings from clinical trials during the reporting period

This section of the PSUR should capture a brief summary of clinically important safety and efficacy findings obtained from the license 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:

(i) Study ID (e.g., protocol number or another identifier)

(ii) Study title

(iii) Study type (e.g., randomized clinical trial, cohort study, case-control study)

(iv) Study population (including country and other relevant population descriptors, e.g., pediatric population or trial subjects with impaired renal function)

(v) Study initiation and completion date (as defined by the manufacturer and/or importer)

(vi) Status: Ongoing or completed

3.5.1.1 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.

3.5.1.2 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.

3.5.1.3 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 for advanced therapy products (e.g. gene therapy, cell therapy products, tissue engineering and biotech products). These are referred to as Advanced Therapy Medicinal Products (ATMPs).

3.5.1.4 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).

3.5.1.5 New safety data related to Fixed Dose Combination therapies

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

(i) 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

(ii) If this PSUR is a combination product, this section should summarize important safety information arising from the individual components

(iii) 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

3.5.2 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.

3.5.3 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.

3.5.4 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:

(i) Pregnancy outcomes (including termination) with or without adverse outcomes

(ii) Use in pediatric populations

(iii) Compassionate supply, named patient use

(iv) Lack of efficacy

(v) Asymptomatic overdose, abuse or misuse

(vi) Medication error where no Adverse Events occurred

(vii) Important non-clinical safety findings

3.6 Information from other clinical trial sources

3.6.1 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).

3.7 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.

3.8 Other Information

This section of PSUR should include the details about signal and Risk Management Plan in place by licence holder (if any) **(For detail, please refer chapter 6)**.

3.8.1 Signal and risk evaluation

In this section, license holder will provide the details of signal(s) and risk(s) identified during the reporting period and evaluation of signals identified during the reporting period.

3.8.1.1 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:

(i) Closed and refuted signal, which would result in the signal being re-opened;

(ii) 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;

(iii) Identified risk for which a higher frequency of the risk is newly found, e.g., in a sub population; and

(iv) 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.

3.8.2 Risk management plan

In this section, license holder will provide the brief details of safety concern and necessary action taken to mitigate these safety concerns.

3.9 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 Syndrome) could reflect a significant risk to the treated population and should be summarized in this section.

3.10 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.

3.11 Overall Safety Evaluation

This section of PSUR should capture the overall safety evaluation of the drug based upon its benefit-risk evaluation for approved indication.

3.11.1 Summary of safety concerns: The purpose of this section is to provide:

(i) Important identified risks

(ii) Important potential risks

(iii) Important missing information

(iv) 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

(v) An evaluation of new information with respect to previously recognized identified and potential risks

(vi) An updated characterization of important potential and identified risks, where applicable and

(vii) 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.

3.11.2 Benefit evaluation

3.11.2.1 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.

3.11.2.2 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.

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

(i) 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

(ii) New information that challenges the validity of a surrogate endpoint, if used

(iii) Clinical relevance of the effect size

(iv) Generalizability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population

(v) Adequacy of characterization of dose-response

(vi) Duration of effect

(vii) Comparative efficacy

A determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

3.11.3 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.

3.11.3.1 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).

A benefit-risk balance 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:

(i) 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.

(ii) 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.

(iii) 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).

(iv) 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.

(v) 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:

(i) The assumptions, considerations, and judgement or weighing that support the conclusions of the benefit-risk evaluation, should be clear.

(ii) If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.

(iii) 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.

3.12 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.

3.13 Appendix

The appendix includes a copy of marketing authorization in India, a copy of prescribing information and line listings of Individual Case Safety Reports with causality assessment.

Chapter-4

Quality Management System at Marketing Authorization Holder Organization

Contents

4 Quality Management System at Marketing Authorization Holder Organization

4.0 Introduction

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

4.1 Scope

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

4.2 Structures and Processes

4.2.1 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).

4.2.2 Quality Management System (QMS) of PV

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

The quality management system is based on the following activities:

(i) Quality planning: Establishing structures of PV system, planning, effective integration and consistent processes for safety

(ii) 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

(iii) Quality control and assurance: By monitoring the parameters described under quality adherence

(iv) Quality improvements: Taking corrective and preventive measures, as and when required, to ensure patient safety

4.2.3 Requirements and Responsibilities of QMS at MAH site

The 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. It should be notified to CDSCO with valid legal documents. The responsibility of adhering to QMS in Pharmacovigilance 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.

4.2.4 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.

4.2.5 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.

4.3 Specific quality system procedures and processes

4.3.1 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:

(i) 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)

(ii) 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)

(iii) 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)

(iv) 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)

(v) Effective communication with regulatory authority, including communication on new or changed risks, the PSMF (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 1 & 5 for detailed information).

4.3.2 Record management

The MAH should 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 of PV records should be at least 10 years.

4.3.3 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).

4.3.4 Critical PV processes

The following PV processes should be considered as critical:

(i) Benefit-risk evaluation

(ii) Establishing, assessing & implementing risk management systems and evaluating the effectiveness of risk minimization

(iii) Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of ICSRs from any source

(iv) Signal management

(v) Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSURs

(vi) Interaction between the PV and product quality defect systems

(vii) Communication about safety concerns between MAHs and licensing authority in particular notifying changes to the benefit-risk balance of pharmaceutical products

(viii) Communicating information to patients and healthcare professionals about changes to the benefit-risk balance of pharmaceutical products with the aim of safe and effective use of pharmaceutical products

(ix) Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the regulatory authority

(x) Implementation of variations to marketing authorizations for safety reasons according to the urgency required

(xi) 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

(xii) Back-up systems for urgent exchange of information within an organization, amongst organizations sharing PV tasks as well as between MAHs and competent authorities

4.3.5 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:

(i) System reviews by those responsible for management

(ii) Audits

(iii) Compliance monitoring

(iv) Inspections

(v) Evaluating the effectiveness of actions taken with pharmaceutical products for the purpose of minimizing risks and supporting their safe and effective use in patients.

(vi) 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 working instructions, deviations from the established quality system, audits and inspections reports as well as the use of the indicators referred to above.

4.3.6 Responsibilities of the PVOIC at MAH Organization

Refer Chapter 1 for detailed information.

Chapter - 5

Audit & Inspection of Pharmacovigilance System at Marketing Authorization Holder Organization

Contents

5 Audit & Inspection of Pharmacovigilance System at Marketing Authorization Holder Organization

5.0 Introduction

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

5.1 Objectives

The objectives of PV audits and inspections are as below:

(i) To verify by examination and evidence, the appropriateness of the implementation and operation of the PV system including its quality systems.

(ii) To assess and establish that the MAH has qualified personnel, robust system and facilities to conduct PV activities

(iii) To identify, record and address non-compliance, which may pose a risk to public health

(iv) 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 a stipulated time period through the implementation of a CAPA plan.

5.2 Inspection Types

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

5.2.1 Routine inspection

These inspections are planned and informed inspection of the PV system at MAH organization. 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 a risk-based approach.

5.2.2 Targeted inspections

These inspections are conducted as and when there is a 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):

(i) Continuous delays or omission and poor-quality reporting of ICSRs/PSURs/RMPs

(ii) Failure to provide the asked information or data within the deadline specified by regulatory authority

(iii) Delays or failure to carry out specific obligations related to the monitoring of pharmaceutical product safety, identified at the time of the marketing authorization

(iv) Delays in the implementation or inappropriate implementation of CAPAs

(v) Sudden pharmaceutical product withdrawal and recall.

(vi) Grievance/complaint pertaining to SAEs

5.3 Inspection Procedure

5.3.1 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 determination of the frequency and scope of inspection to be carried out.

The inspection will be planned based on the following:

(i) Compliance history identified during previous PV inspections.

(ii) Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection

(iii) 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

(iv) 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

(v) Changes in contractual arrangements with PV service providers or the organizations at which PV activities are conducted

(vi) Delegation or transfer of PSMF management

(vii) Change of PVOIC since the last inspection

During inspection the parameters for the inspection will include overseeing the overall PV system of MAH. A notice will be given to the MAH before scheduled inspection except the for-cause/surprise inspection.

5.3.2 Organization to be inspected

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

5.3.3 Inspection procedures

The inspection procedures depend on the nature (routine/targeted) of the inspection and the conditions of inspection request. All the necessary PV documents should be submitted to the inspectors during inspection. When necessary, the inspectors may also request other documents related to the inspection, including job descriptions of PV personnel, products and company related information etc. They shall also conduct interviews of the relevant persons involved in different PV activities. Inspection should be carried out to examine compliance with Drugs and Cosmetics Act, 1940 and NDCT Rules 2019.

5.3.4 Inspection findings

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

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

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

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

5.3.5 Inspection follow-up

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

(i) Review of the MAH's CAPA plan

(ii) Review of the periodic progress reports, when deemed necessary

(iii) Re-inspection to assess appropriate implementation of the corrective and preventive action plan

(iv) Requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities

(v) Requests for issuing safety communications including amendments of marketing and/or advertising information

(vi) Communication of the inspection findings to other regulatory authorities (including outside India)

(vii) Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions related to the marketing authorizations or clinical trial authorizations)

5.3.6 Responding to inspection findings

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

5.4 Regulatory actions

When a non-compliance to the PV regulatory obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. In the event of non-compliance, possible regulatory options include the following:

(i) Suspension/Cancellation/Withdrawal of marketing authorization

(ii) Restriction on approvals of new marketing authorization applications

(iii) Product recalls

(iv) Updating of Prescribing Information Leaflets/SmPCs

5.5 Training of Inspectors

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

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

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

Chapter - 6

Submission of Risk Management Plan

Contents

6 Submission of Risk Management Plan

6.0 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 a 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.

6.1 Objectives

(i) Identification and characterization of risk to update the safety profile of the pharmaceutical product(s)

(ii) Indicate how to characterize further the safety profile of the pharmaceutical product(s)

(iii) Document measures to prevent or minimize the risks associated with a pharmaceutical product, including an assessment of the effectiveness of interventions

(iv) Document post-marketing obligations that have been imposed as a condition of the marketing authorization

(v) 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 product.

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 Risk Management Plan

6.2.1 Pharmaceutical product overview

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

(i) 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.

(ii) Information on the excipients used in the formulation of a pharmaceutical product should be provided.

(iii) 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 and 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, further characterization of 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, Prescribing Information Leaflet (PIL), pack size and risk minimization activities. The MAH should also consider when it is appropriate to have additional risk minimization activities like educational material, communication letter to HCPs etc.

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

(i) Objectives of the risk minimization activities

(ii) Routine risk minimization activities

(iii) Additional risk minimization activities (if any), individual objectives and justification

(iv) How the effectiveness of each (or all) risk minimization activities will be evaluated in terms of attainment of their stated objectives?

(v) What the target is for risk minimization? i.e. what are the criteria for judging success?

(vi) Milestones for evaluation and reporting

References

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10. New Drugs and Clinical Trials Rules, 2019.

APPENDICES

Appendix-A	**WHO Causality Assessment Scale**
Appendix-B	**Examples of summary tabulations in PSUR**
Appendix-C	**Summary of safety signals that were ongoing or closed during the reporting interval (From DD-MM-YYYY to DD-MM-YYYY)**
Appendix-D	**Definitions**
Appendix-E	**Frequently Asked Questions (FAQs)**

Appendix - A

WHO Causality Assessment Scale

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by diseases 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 plausible time relationship to drug intake • Unlikely to be attributed to diseases 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 be explained by diseases 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 make a relationship improbable (but not impossible) • Diseases 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 • Can not be judged because information is insufficient or contradictory • Data can not be supplemented or verified

Appendix - B

Examples of summary tabulations in PSUR

Table 1 : Estimated cumulative subject exposure from Clinical Trials

Treatment	Number of subjects
Pharmaceutical product	
Comparator	
Placebo	

Table 2 : Cumulative subject exposure to new drug from Clinical Trials by age and sex

	Number of subjects		
Age range	Male	Female	Total

Table 3 : 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	

Table 4 : Cumulative exposure from marketing experience from India

Indication	Gender		Age				Dose (mg/day)			Formulation		
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others
Overall												
e.g. Fever												
e.g. Migraine												

Table 5 : Interval exposure from marketing experience from India

Indication	Gender		Age				Dose (mg/day)			Formulation		
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others
e.g. Fever												
e.g. Migraine												

Table 6 : Cumulative exposure from marketing experience Rest of the World (whichever applicable)

Indication	Gender		Age				Dose (mg/kg)			Formulation			Rest of the world		
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others	Japan	USA	Other
Overall															
e.g. Fever															
e.g. Migraine															

Table 7 : Interval exposure from marketing experience from Rest of the World (whichever applicable)

Indication	Gender		Age				Dose (mg/kg)			Formulation			Rest of the world		
	Male	Female	2 to 16	> 16 to 65	> 65	Unknown	< 40	≥ 40	Unknown	Intravenous	Oral	Others	Japan	USA	Other
e.g. Fever															
e.g. Migraine															

Table 8 : Cumulative tabulations of serious Adverse Events from clinical trials

System Organ Class (SOC) Preferred Term (PT)	Investigational pharmaceutical product	Blinded	Active comparator	Placebo
e.g. Blood and lymphatic system disorders				
e.g. Anaemia				
e.g. Bone marrow necrosis				
e.g. Cardiac disorder				
e.g. Tachycardia				
e.g. Ischemic cardiomyopathy				

Table 9 : Number of ADRs from Post marketing sources

System Organ Class (SOC)	Spontaneous including regulatory authority and literature					Non-interventional post marketing study and reports from other solicited sources	
Preferred Term (PT)	Serious		Non serious		Total	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
SOC 1							
PT							
SOC 2							
PT							

Appendix - C

Summary of safety signals that were ongoing or closed during the reporting interval (From DD-MM-YYYY to DD-MM-YYYY)

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signal)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
e.g. Stroke	MM/YYYY	Ongoing	MM/YYYY	Meta analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
e.g. Stevens Johnson Syndrome	MM/YYYY	Closed	MM/YYYY	Spontaneous case reports	Rash already in identified, SJS not reported in clinical trial	Targeted follow up of reports with site visit to one hospital. Full review of cases by dermatologist and literature searches	RSI updated with a warning & precautions

Appendix - D
Definitions

1. Adverse Drug Reaction

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

2. Adverse Event

Adverse event means any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug or a pharmaceutical product in a patient or a trial subject that does not necessarily have a relationship with the treatment being given.

3. Benefit-Risk Analysis

Examination of the favourable (beneficial) and unfavourable results of undertaking a specific course of action. (While this phrase is still commonly used, the more logical pairings of benefit harm and effectiveness-risk are slowly replacing it).

4. Causality Assessment

The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event. Causality assessment is usually made according to established algorithms.

5. Company Core Data Sheet (CCDS)

A document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.

6. 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.

7. Clinical Trial

Academic Clinical Trial means a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose.

8. 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:

(i) An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;

(ii) 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;

(iii) 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.

9. 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.

10. Investigational Drug

The term investigational drug is used in this guideline to indicate only the experimental product under study or development

11. New Drug

According to New Drugs and Clinical Trials Rules, 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

(iv) 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

(v) a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

(vi) 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;

(vii) **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.

12. 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.

13. Post-Marketing

The stage when a drug is generally available on the market.

14. 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

(i) Observed or resolved in clinical studies; adverse events observed in clinical trials or

(ii) 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

(iii) Products of the same class or which could be expected to occur based on the properties of the medicinal product.

15. Periodic Safety Update Report

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.

16. 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).

17. Serious Adverse Event

A serious adverse event or reaction is any untoward medical occurrence at any dose that results in;

(i) Death

(ii) Life threatening

(iii) Hospitalization – Initial/Prolonged

(iv) Congenital anomaly

(v) Disability

(vi) Other medically important Event

18. 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.

19. 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.

20. 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.

21. 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.

22. Summary of Product Characteristics (SmPCs)

A regulatory document attached to the marketing authorization which forms the basis of the product information made available to prescribers and patients.

Appendix - E

Frequently Asked Questions (FAQs)

Q.1 The MAH should submit serious ADRs in E2B-XML (R2 or R3) format via emails: pharma.covig@cdsco.nic.in and mah.nccpvpi-ipc@gov.in within 15 days of initial receipt of the information. PvPI requires the Company ICSR report number, Seriousness, Initial/Follow-up number should be mentioned in the email and XML E2B (R2 or R3) format file name ID while submitting safety reports. Is it correct?

Ans. **Yes**, the MAH should submit serious ADRs in E2B-XML- (R3) format via email: pharma.covig@cdsco.nic.in and mah.nccpvpi-ipc@gov.in within 15 days of initial receipt of the information. The ICSR's report number, Seriousness should be mentioned in the email and Initial/Follow-up number in file name/ID of E2B XML (R3) format.

Q.2 The MAH should submit non-serious ADRs in E2B, XML- (R2 or R3) format to: : pharma.covig@cdsco.nic.in and mah.nccpvpi-ipc@gov.in within 30 days of initial receipt of the information. PvPI requires the Company ICSR report number, Seriousness, Initial/Follow-up number should be mentioned in the email and E2B-XML (R2 or R3) format file name ID when submitting safety reports. Is it correct?

Ans. **Yes**, As per this PV Guidance Document for MAHs of Pharmaceutical Products, Version 2.0, all non-serious Adverse Events in E2B, XML format (R3) must be reported within 90 calendar days to PvPI. The ICSR's report number, seriousness should be mentioned in the email and Initial/Follow-up number in file name/ID of E2B XML (R3) format.

Q.3 Can the MAHs directly upload the ICSRs into VigiFlow?

Ans. **No**, PvPI, IPC has not given direct Gateway access to MAHs at their site for uploading ICSRs.

Q.4 Is full text of the literature article is required in English for the reporting of literature case to PvPI?

Ans. **Yes**, it is required to verify the literature case.

Q.5 What is timeline for the reporting of Serious Unexpected Adverse Reactions to the PvPI & Licensing Authority by the applicant?

Ans. All Serious Adverse Events should be reported to the PvPI & Licensing Authority within 15 calendar days of initial receipt of the information by the applicant.

Q.6 What is the timeline for the reporting of non-serious AEs/ADRs to the NCC-PvPI, IPC by the MAHs?

Ans. All non-serious AEs/ADRs should be reported to the NCC-PvPI, IPC, within 90 calendar days of initial receipt of the information by the MAHs.

Q.7 If, the pharmaceutical company has marketing authorization in India and it has registered its products in state FDA, does ICSRs submission required?

Ans. **Yes**, submission of ICSRs is required for all pharmaceutical products marketed or imported in India.

Q.8 Is Periodic Safety Update Report (PSUR) submission is required for Generic Products?

Ans. **No**, PSUR must be submitted as per the NDCT Rules, 2019 for the New Drugs marketed in India.

Q.9 If any MAH is submitting ICSR in E2B XML (R3) format for their pharmaceutical products to PvPI, do they still need to submit ICSR in CIOMS format to PvPI or CDSCO, as part of regulatory submission?

Ans. The PvPI requires the submission of ICSRs in E2B, XML format by MAHs. Therefore, there is no need to submit the same ICSR in CIOMS format. You may submit it to the CDSCO.

Q.10 Is there any requirement to submit the foreign post-marketing ICSRs by Marketing Authorisation Holder to the NCC-PvPI, IPC?

Ans. No, PvPI requires the reporting of ICSRs for the marketed/imported pharmaceutical products in India.

NCC - PvPI Helpline

1800-180-3024

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Pharmacovigilance Programme of India
Ministry of Health & Family Welfare, Govt. of India
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For any relevant Information/Suggestions/Query

Please Contact: Officer-in-Charge, Pharmacovigilance Programme of India
Email: mah.nccpvpi-ipc@gov.in, lab.ipc@gov.in website: www.ipc.gov.in