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SCHOOL OF BIO AND CHEMICAL ENGEERING

DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES

(INTERNATIONAL RESEARCH CENTRE)

UNIT – I - General overview of Pharmacovigilance – SMB5401

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY

CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES
COURSE MATERIAL

Subject Name: Pharmacovigilance and Safety monitoring **Subject Code: SMB5401**

UNIT – I

General overview of Pharmacovigilance

Introduction- Definition

Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is "defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines." Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. While major advancements of displine of pharmacovigilance have taken place in the western countries not much has been achieved in India. There is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. This will enable integration of good pharmacovigilance practice in the process and procedures to help ensure regulatory compliance and enhance clinical trials safety and post marketing surveillance.

Aims of Pharmacovigilance

1. Improve patient care and safety in relation to the use of medicines and all medical and Para medical interventions

2. Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.

3. Pharmacovigilance keeps track of any drastic effects of drugs.

4. Improve public health and safety in relation to the use of medicines.

5. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.

6. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

Adverse Drug Reaction (ADR) in Pharmacovigilance

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

An appreciably harmful or unpleasant reaction, caused by an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

Any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility, necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death.

Harm directly caused by a drug at normal doses.

Adverse Drug Event (ADE)

Any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment.

Injuries caused by medical interventions related to a drug.

Adverse drug events may result from medication errors o from ADRs in which there was no error (Bates)d

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug (Cobert)e

Serious Adverse Effect

Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening.

Signal

Reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented.

Medication Error

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer

Errors in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present.

Inappropriate use of a drug that may or may not result in harm.

Types of Adverse Drug Reactions (Rawlins and Thompson Classification)

Typtes A Effects

1.Due to pharmacological effects.

2.Are dose related – may often be avoided by using doses which are appropriate to the individual patient.

3.Example: hypnotic effect after H2 antihistaminics.

Types B Effects

1.Generally rare and unpredictable.

2.Occur in predisposed, intolerant patients – can be explained by rare genetic polymorphism, allergic reactions.

3.Example: Penicilline allergies.

Types C Effects

1.Adverse reactions after long term therapy.

2.There is often no suggestive time relationship and the connection may be very difficult to prove. The use of a drug increases the frequency of "spontaneous" disease.

3.Example: carcinogenesis.

Types D Effects

1.Adverse effect may be presented years after a drug was used.

2.Example: Vagina cancer of daughters when their mother was treated by diethylstilbestrol.

Types E Effects

1.Absence of drug after withdrawal – rebound effect.

2.Example: corticosteroids in asthma treatment.

Signal and detection of signal

Signal detection and its assessment is the most important aspect of pharmacovigilance. The WHO defines a signal as: 'Reported information on a possible causal relationship between an adverse event and a drug, of which the relationship is unknown or incompletely documented previously'. Often, a limited number of reports represent a signal. These signals are reported to regional pharmacovigilance centres followed by zonal centres. Finally, all case reports are filed in databases at the National Centres as well as sent onto the WHO Collaborating Centre for International Drug Monitoring (the Upsala Monitoring Centre). Further, signal assessment is performed using Upsala Monitoring scale (UMC) & Naranjo scale of probability to analyse the cause and effect analysis. Signal detection and its assessment is very vital and complex process.

The early detection of safety signals as soon as possible is increasingly important and of great interest to the pharmaceutical industry, regulators, and the public domain. Signals have both qualitative and quantitative aspects. Different categories of adverse events need different

methodologies for detection. The primary function of pharmacovigilance is early detection of signals. In 1960s, thalidomide tragedy occurred due to late signal detection. However, spontaneous reporting systems have now been developed and used all around the world. The number of case reports received by the World Health Organization (WHO-UMC) collaborating Centre for International Drug Monitoring in Uppsala, Sweden is continuously rising and now numbers almost 2,00,000 per year. The safety signals are generated by various sources such as spontaneous reporting, case control and cohort studies, pre-clinical as well as clinical studies.

Signals can also be identified by major statistical algorithms and advanced analysis in conjunction with biostatistics. Commercial tools are also available for data mining and signal detection and analysis. Signal detection consists of several activities:

Signal detection tools:

single case evaluation, including literature surveillance

aggregate report creation

software tools for large case volumes and trend analysis

Signal generation/detection procedure:

permanent monitoring of single case reports/report series

periodic report review e

ad hoc analysis of reports from external sources, e.g. literature reports, requests from competent authorities (CAs) on report/reports

Signal work-up and documentation:

quality of the information e other risk factors (e.g. natural history of the underlying disease/severity, specificity and outcome)

biological and pharmaceutical plausibility

class effect

epidemiological context

frequency

drug utilization/population exposure/age, gender and indication

Signal assessment and documentation:

QPPV or other senior pharmacovigilance involvement/decision

signal not confirmed (no further actions, only documentation)

signal doubtful (special scrutiny for future cases)

signal confirmed.

Upon confirmation of a safety signal, the subsequent course will be variable but may involve action by company executives and/or the regulatory authorities, depending on the magnitude of risk. It is important that action is taken promptly in order to avoid any unnecessary harm; therefore, an ongoing and systematic approach is essential. For safety findings that have low or minimal safety impact, these will be reported in the clinical study report (clinical trials), in updates to the investigator brochure, in the core data sheet, or in periodic safety update reports required by the regulatory authorities. The conclusion of any update report must comment on any new safety issue. Reports may be written within the pharmacovigilance department or by a medical writing team, with input from pharmacovigilance staff. In the case of marketed products, changes to labeling may be required. All of this is part of the communication of any safety risk to those who might use the product.

Monitoring and management of adverse drug reactions

Monitoring in the sense described is used in three different aspects of the therapeutic process. Clinicians and patients themselves, can monitor response to treatment of a specific condition – for example, monitoring the temperature during antibacterial treatment. If a drug has a narrow therapeutic range, samples can be taken to allow the dose to be adjusted so that the concentration remains between a minimum value for efficacy and a maximum value for safety. Monitoring for adverse effects by repeated laboratory testing seems to have begun with the

observation that the antibacterial drug chloramphenicol could cause bone-marrow toxicity of two types, one of which occurred at high dosage and was reversible, and the other of which could occur at any therapeutic dosage and generally resulted in fatal aplastic anaemia.

Monitoring is a process of checking a system that changes with time, in order to guide changes to the system that will maintain it or improve it. A recent article discussing the monitoring of disease in medicine has drawn attention to the more general problem of monitoring the health of patients suffering with chronic disease. These examples illustrate monitoring by observing directly the quantity of interest, but indirect (surrogate or proxy) measures are also widely used. The choice of surrogate measure is important, as the surrogate needs to reflect closely the reaction of interest. Development of better surrogate measures to aid monitoring of disease and its response to therapy is dependent upon an understanding of the chain of events in the pathogenesis of disease through to its final clinical end-point.

The advice on haematological monitoring given to prescribers might be expected to reflect difficulties such as these, noted over 25 years ago. However, many Summaries of Product Characteristics provide instructions for monitoring for haematological adverse reactions that are incomplete or impractical in modern clinical settings.

Management

Rapid action is sometimes important because of the serious nature of a suspected adverse drug reaction, for example anaphylactic shock. Otherwise, using clinical benefit-risk judgment, together with help from investigations, one decides which medicine or medicines should be withdrawn as a trial. The patient should be observed during withdrawal. The waiting period will vary, depending on the rate of elimination of the drug from the body and the type of pathology. For example, urticaria usually disappears quickly when the drug is eliminated, whereas fixed psoriatic skin reactions can take weeks to resolve. If the patient is clearly getting better, If the patient cannot manage without a medicine that has caused an adverse reaction, provide symptomatic relief while continuing the essential treatment.

Diagnosis

The diagnosis of an adverse drug reaction is part of the broader diagnosis in a patient, if a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction the first problem is to find out whether a patient is taking a medicinal product, including: over-the-counter formulations; products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse); and long-term treatments that the patient may forget (such as oral contraceptives). The next step is to find out whether the effect could be due to a medicine, if the patient is taking several medicines, the problem is to distinguish which, if any, is causative, this problem is complex, because some of the patient's complaints might be due to other diseases or to one or more of the drugs, there are many formal methods for assigning robability of causation to a suspected adverse drug reaction.

Factors affecting adverse drug reaction

1. Patient related factors

a Age

All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. Age is a very important factor which affects the occurrence of ADRs. Elderly patients with multiple medical problems who are taking multiple drugs, those who have a history of ADRs, and those with a reduced capacity to eliminate drugs are at high risk for ADRs. Infants and very young children are at high risk of ADRs because their capacity to metabolize the drug is not fully evaluated. The following are some factors that might affect the development of ADRs in neonates.

1. Neonates have immature renal tubular function when they are below the age of 8 weeks, avoiding digoxin, aminoglycosides, ACE inhibitors, NSAIDs is a must.

2. Physiologic hypoalbuminemia in neonates affects drug dosing. Caution is recommended when dealing with high protein binding drugs such as NSAIDs.

3. Neonates, have low body fat; they might be affected by fat soluble drugs.

4. Increased anesthetic effects due to immature blood brain barrier at < 8 weeks of age.

5. Predisposition to hypotension due to poor cardiac compliance and immature baroreceptors.

b. Gender

The biological differences of males and females affect the action of many drugs, the anatomical and physiological differences are body weight, body composition, gastrointestinal tract factors, liver metabolism, and renal function, women in comparison to men have lower bodyweight and organ size, more body fat, different gastric motility and lower glomerular filtration rate. They also suggested that women are more prone than men to develop torsade de pointes ventricular tachycardia during the administration of drugs that prolong cardiac repolarization. Women restrict their activity because of acute and chronic health problems approximately 25% more days per year than do men, spending approximately 40% more days in bed each year than men.

c. Maternity status

Pregnancy has an impact on drug treatment. Not only are women affected by the drug, but the fetus will also be exposed to ADRs of the drug, acidity and tone of GIT are decreased during pregnancy and this might interfere with drug absorption or excretion and finally drug metabolism may be affected at certain stages of pregnancy. Many drugs for example, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers pose a risk to the health and normal development of a fetus.

d. Allergy

Drug independent cross-reactive antigens can induce sensitizations, which can manifest as a drug allergy. The existence of such cross-reactivity is supported by medical literature corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I or IV reactions; type II and III reactions are only encountered infrequently.

e. Body weight and fat distribution

In the body, drugs are distributed to and from the blood and various tissues of the body (for example, fat, muscle and brain tissue), after a drug is absorbed into the bloodstream, it rapidly circulates through the body, as the blood recirculates, the drug moves from the bloodstream into the body's tissues, once absorbed, most drugs do not spread evenly throughout

the body.[39] Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug.

Periodic Safety Update Report (PSUR)

The PSUR can be an important source for the identification of new safety signals. A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to the Competent Authorities at defined time points post-authorisation. PSURs must be submitted for all registered products, regardless of their marketing status. A single report may cover all products containing the same active substance(s) licensed by one marketing authorisation (MA) holder.

Individual case safety reports (ICSRs)

Individual Case Safety Report (ISCR) is a document providing the most complete information related to an individual case at a certain point of time. ICSRs, sometimes referred to as safety reports, are used for reporting suspected adverse reactions to the EudraVigilance database to a medicinal product that occur in a single patient at a specific point in time. An individual case is the information provided by a primary source to describe suspected adverse reactions/suspected unexpected serious adverse reactions related to the administration of one or more medicinal products/investigational medicinal products to an individual patient at a particular point of time.

Spontaneous reporting

It is defined as "A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national pharmacovigilance centre".

It has two steps:

1. **Data acquisition –** depends largely on the input of information derived from reports submitted by the health professionals

2. **Data assessment** – involves assessment of the individual case reports and assessment of pooled data obtained from various sources such as the international database of the WHO.

3. **Data Interpretation –** involves interpreting the data obtained from data acquisition and data assessment

At present, post-marketing surveillance of medicines is mainly co-ordinated by national pharmacovigilance centres. In collaboration with the Uppsala Monitoring Centre (UMC) the National Centres have achieved a great deal in:

Collecting and analysing case reports of ADRs

Distinguishing signals from background 'noise'

Making regulatory decisions based on strengthened signals

Alerting prescribers, manufacturers and the public to new risks of adverse reactions.

The number of National Centres participating in the WHO International Drug Monitoring Programme has increased from 10 in 1968 when the Programme started to 67 in 2002. The centres vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

National pharmacovigilance centres are responsible for:

Promoting the reporting of adverse reactions;

Collecting case reports of adverse reactions;

Clinically evaluating case reports;

Collating, analyzing and evaluating patterns of adverse reactions;

Distinguishing signals of adverse reactions from "noise";

Recommending or taking regulatory action in response to ?ndings supported by good evidence;

Initiating studies to investigate significant suspect reactions;

Alerting prescribers, manufacturers and the public to new risks of adverse reactions; and

Sharing their reports with the WHO Programme for International DrugMonitoring.

What to report

The National Pharmacovigilance Programme (NPP) shall encourage reporting of all suspected drug related adverse events, including those suspected to have been caused by herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions would be important since it may highlight a widespreadprescribing problem.

The programme particularly solicits reports of:

All adverse events suspected to have beencaused by new drugs and 'Drugs of current interest'

All suspected drug interactions

Reactions to any other drugs which are suspected of significantly affecting a patient's management,

including reactions suspected of causing:

Death

Life-threatening (real risk of dying)

Hospitalisation (initial or prolonged)

Disability (significant, persistent or permanent)

Congenital anomaly

Required intervention to prevent permanent impairment or damage

Who can report

Any health care professionals (Doctors including Dentists, Nurses, and Pharmacists) may report suspected adverse drug events. The Programme shall not accept reports from lay members of the public or anyone else who is not a health care professional.

Where to report

After completion the form shall be returned/forwarded to the same pharmacovigilance Centre from where it was received. Reporting can be done to any one of the country vide pharmacovigilance Centres nearest to the reporter. (Complete list of pharmacovigilance Centres is available at www.cdsco.nic.in) In case of doubt the form may be sent to the national pharmacovigilanc Centre at: Central Drugs Standard Control Organisation, New Delhi.

What happens to the information submitted

The information in the form shall be handled in strict confidence. Peripheral Pharmacovigilance Centres shall forward the form to the respective Regional Pharmacovigilance Centres who will carry out the causality analysis. This information shall be forwarded to the Zonal Pharmacovigilance Centres. The data will be statistically analysed and forwarded to the global Pharmacovigilance Database managed by WHO Uppsala Monitoring Centre in Sweden. The final report based on the analysed data will be periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review data and suggest any regulatory interventions that may be required with respect to the drug/drugs or class of drugs.

Risk evaluation and mitigration strategy (REMS)

The Risk Mangement Plan (EU) and the REMS (USA) are now a standard part of pharmacovigilance planning. ICH E2E (Pharmacovigilance Planning) was originally created to achieve consistency and harmonization, particularly during the early postmarketing period of medicinal products. Within the past few years, the US and European regulatory agencies have increased their guidance on benefit risk assessment and risk minimization.

The intent of both the RMP and the REMS is to minimize risks related to a medicinal product through interventions and to communicate those risks to patients and healthcare providers. Elements may include medication guides or patient package inserts, a detailed communication plan about safety issues, specific elements to assure safe use of a product such as required laboratory testing or prescriber training, an implementation plan and a timetable for assessment.

Currently, the RMP or REMS may be created at any time during clinical development, but most often they are submitted as part of the marketing application. In the EU, RMPs are routinely required as part of the detailed description of the pharmacovigilance system. In the USA, the regulatory authorities can request a plan if there is a reason to suspect that one may be necessary, based upon non-clinical data, early use data, class data for the medicinal compound, or other factors.

If new safety information becomes available after regulatory approval, the regulatory authorities may request a REMS or an updated RMP. Additional pharmacovigilance such as active surveillance, other clinical or epidemiological trials, specialized training, or restricted access may be included in the plan. The activities must be sufficient to minimize the likelihood of harm so that benefits still outweigh risks, and to ensure that the risk reduction procedures are communicated and implemented.

In determining whether REMS is necessary, the law requires the consideration of the following factors:

the estimated size of the population likely to use the drug involved,

the seriousness of the disease or condition that is to be treated with the drug,

the expected benefit of the drug with respect to such disease or condition,

the expected or actual duration of treatment with the drug,

the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity.

Elements of REMS

An approved REMS must include a timetable of when the manufacturer will provide reports to FDA to assess the effectiveness of the REMS components; this includes an assessment, at minimum, by 18 months, three years, and in the seventh year after the REMS is approved, or as otherwise specified. The assessment requirement may be removed after three years if FDA determines that the risks of the drug have been adequately identified, assessed, and

managed. In addition to the required timetable of assessments, a REMS may include the following elements:

Patient Information:

The REMS may require the manufacturer to develop materials for distribution to each patient when the drug is dispensed. This could be a Medication Guide, as provided for under FDA regulations, or a patient package insert. In 2011 guidance, FDA determined that it was no longer necessary to consider every Medication Guide to be an element of a REMS. The updated FDA policy allowed manufacturers with REMS that included only a Medication Guide and a timetable for assessment (and no ETASU) to request a modification to eliminate the REMS; however, a Medication Guide could still be required under FDA regulations.

Communication Plan:

The REMS may require the manufacturer to create a communication plan, which could include sending letters to health care providers; disseminating information to providers about REMS elements to encourage implementation or explaining safety protocols; or disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use.

ETASU:

An ETASU is a restriction on distribution or use that is intended to (1) allow access to those who could benefit from a drug while minimizing the risk of adverse events, and (2) block access to those for whom the risks would outweigh the potential benefits. For example, an ETASU could require that pharmacies, practitioners, or health care settings that dispense the drug be specially certified, or that the patient using the drug be subject to monitoring (e.g., regular pregnancy testing for a drug associated with birth defects). By including such restrictions, FDA is able to approve a drug that it otherwise would have to keep off the market due to safety issues.

Implementation System:

The REMS may include an implementation system related to ETASU through which the manufacturer may be required to take reasonable steps to monitor and evaluate those in the health care system (e.g., doctors, pharmacists) responsible for implementing the ETASU.

Significance of Pharmacovigilance

Pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines, all of vitamins unpredictable potential for harm. When adverse effects and toxicity do appear especially when previously unknown it is essential that these are reported, analysed and their significance communicated effectively to an audience that has the knowledge to interpret the information. Which carry an inevitable and some-For all medicines there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To achieve this is to:

- Serve public health, and to foster a sense of trust among patients in the medicines they use that would extend to confidence in the health service in general;
- Ensure that risks in drug use are anticipated and managed;
- Provide regulators with the necessary information to amend the recommendations on the use of the medicines;
- Improve communication between the health professionals and the public;
- Educate health professionals to understand the effectiveness/risk of medicines that they prescribe. This is the significance role pharmacovigilance.

Question Bank

1. Explain the classification of ADRs.

2. Detail about role of pharmacovigilance in clinical trial

3. What are the methods of pharmacovigilance

4. Write about the ADR report journey process

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UNIT – II - Pharmacovigilance and ICH guideline – SMB5401

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COURSE MATERIAL

Subject Name: Pharmacovigilance and Safety monitoring **Subject Code: SMB5401**

UNIT - II

ICH Topic E 2 A
Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

NOTE FOR GUIDANCE ON CLINICAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS
FOR EXPEDITED REPORTING
(CPMP/ICH/377/95)

APPROVAL BY CPMP	November 1994
DATE FOR COMING INTO OPERATION	June 1995

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

ICH Harmonised Tripartite Guideline

1. INTRODUCTION

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models. However, there are special circumstances involving medicinal products under development, especially in the early stages and before any marketing experience is available. Conversely, it must be recognised that a medicinal product will be under various stages of development and/or marketing in different countries, and safety data from marketing experience will ordinarily be of interest to regulators in countries where the medicinal product is still under investigational-only (Phase 1, 2, or 3) status. For this reason, it is both practical and well-advised to regard pre-marketing and post-marketing clinical safety reporting concepts and practices as interdependent, while recognising that responsibility for clinical safety within regulatory bodies and companies may reside with different departments, depending on the status of the product (investigational vs. marketed).

There are two issues within the broad subject of clinical safety data management that are appropriate for harmonisation at this time:

1. the development of standard definitions and terminology for key aspects of clinical safety reporting, and

2. the appropriate mechanism for handling expedited (rapid) reporting, in the investigational (i.e., pre-approval) phase.

The provisions of this guideline should be used in conjunction with other ICH Good Clinical Practice guidelines.

2. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [Edwards, I.R., et al, Harmonisation in Pharmacovigilance. *Drug Safety* 10(2): 93-102, 1994.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

1. Adverse Event (or Adverse Experience)

> *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

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

2. Adverse Drug Reaction (ADR)

In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

> *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.*

The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding *marketed medicinal products*, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

> *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.*

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

3. Unexpected Adverse Drug Reaction

> *An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). (See section III.C.)*

B. Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

> The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

> *A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
>
> - *results in death,*
> - *is life-threatening,*
>
> NOTE*:*The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
>
> - *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
> - *results in persistent or significant disability/incapacity, or*
> - *is a congenital anomaly/birth defect.*

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

C. Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition (II.A.3.), an "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)

2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

3. STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.

Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to *expedited* reporting.

Information obtained by a sponsor or manufacturer on serious, unexpected reports from any source should be submitted on an expedited basis to appropriate regulatory authorities if the minimum criteria for expedited reporting can be met. See section III.B.

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

2. Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgement should be applied for each situation. In general, information that might

materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

a) For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

b) A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.

c) A major safety finding from a newly completed animal study (such as carcinogenicity).

B. Reporting Time Frames

1. Fatal or Life-Threatening Unexpected ADRs

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation, or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigations program. Fatal or life-threatening, unexpected ADRs occurring in *clinical investigations* qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

2. All Other Serious, Unexpected ADRs

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

3. Minimum criteria for reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an identifiable patient; a suspect medicinal product; an identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Follow-up information should be actively sought and submitted as it becomes available.

C. How to Report

The CIOMS-I form has been a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain basic information/data elements, when available, be included with any expedited report, whether in a tabular or narrative presentation. The listing in Attachment 1 addresses those data elements regarded as desirable; if all are not available at the time of expedited reporting, efforts should be made to obtain them. (See section III.B.)

All reports must be sent to those regulators or other official parties requiring them (as appropriate for the local situation) in countries where the drug is under development.

D. Managing Blinded Therapy Cases

When the sponsor and investigator are blinded to individual patient treatment (as in a double-blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

There are several disadvantages to maintaining the blind under the circumstances described which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised. If the event is serious, new, and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

E. Miscellaneous Issues

1. Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies. Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

2. Products with More than one Presentation or Use

To avoid ambiguities and uncertainties, an ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.

It is not uncommon that more than one dosage form, formulation, or delivery system (oral, IM, IV, topical, etc.) of the pharmacologically active compound(s) is under study or marketed; for these different presentations there may be some marked differences in the clinical safety profile. The same may apply for a given product used in different indications or populations (single dose vs. chronic administration, for example). Thus, "expectedness" may be product or product-use specific, and separate Investigator's Brochures may be used accordingly. However, such documents are expected to cover ADR information that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information will also be included.

It is recommended that any adverse drug reactions that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of overreporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.

3. Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

F. Informing Investigators and Ethics Committees/Institutional Review Boards of New Safety Information

International standards regarding such communication are discussed within the ICH GCP Guidelines, including the addendum on "Guideline for the Investigator's Brochure." In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in accord with any local regulatory requirements, so as to keep the description of safety information updated.

ATTACHMENT 1

KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details

Initials

Other relevant identifier (clinical investigation number, for example)

Gender

Age and/or date of birth

Weight

Height

2. Suspected Medicinal Product(s)

Brand name as reported

International Non-Proprietary Name (INN)

Batch number

Indication(s) for which suspect medicinal product was prescribed or tested

Dosage form and strength

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)

Route of administration

Starting date and time of day

Stopping date and time, or duration of treatment

3. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

Start date (and time) of onset of reaction

Stop date (and time) or duration of reaction

Dechallenge and rechallenge information

Setting (e.g., hospital, out-patient clinic, home, nursing home)

Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR)

Name

Address

Telephone number

Profession (speciality)

6. Administrative and Sponsor/Company Details

Source of report: was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other?

Date event report was first received by sponsor/manufacturer

Country in which event occurred

Type of report filed to authorities: initial or follow-up (first, second, etc.)

Name and address of sponsor/manufacturer/company

Name, address, telephone number, and FAX number of contact person in reporting company or institution

Identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA number)

Sponsor/manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).

ICH Topic E 2 C (R1)
Clinical Safety Data Management:
Periodic Safety Update Reports for Marketed Drugs

Step 5

NOTE FOR GUIDANCE ON CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS
(CPMP/ICH/288/95)

TRANSMISSION TO CPMP	December 1995
TRANSMISSION TO INTERESTED PARTIES	December 1995
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CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

ICH Harmonised Tripartite Guideline

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PART I
CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

1. INTRODUCTION

1.1 Objectives of the guideline

The main objective of ICH is to harmonise technical requirements for marketing authorisation. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (EU, Japan, USA). In order to avoid duplication of effort and to ensure that important data is submitted with consistency to regulatory authorities, this guideline on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed*.

1.2 Background

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialisation. Surveillance of marketed drugs is a shared responsibility of the Regulatory Authorities and Marketing Authorisation Holders (MAH). They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the worldwide safety experience of a medicinal product at defined times post-authorisation, in order to:

- report all the relevant new safety information from appropriate sources;
- relate these data to patient exposure;

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* Guidelines are not legally binding. Some portions of this guideline may not be reflected in existing regulations. To that extent, until the regulations are amended, MAHs must comply with existing regulations.

- summarise the market authorisation status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety reevaluation;
- indicate whether changes should be made to product information in order to optimise the use of the product.

However, if the PSURs required in the different countries where the product is on the market require a different format, content, period covered and filing date, MAH would be required to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonise the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The U.S regulations require quarterly reports during the first 3 years, then annual reports. The FDA has recently published proposed rules[1] which take into account the CIOMS Working Group II proposals[2].
- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorisation. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabeled must be reported every 6 months for 3 years and annually thereafter.

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented. Appended is a glossary of important relevant terms.

1.3 Scope of the guideline

This guideline on the format and content of periodic safety update reports (PSURs) is considered particulary suitable for comprehensive reports covering short periods (e.g. six months, one year) often prepared during the initial years following authorisation.

This guideline might also be applicable for longer term reporting intervals; however, other options may be appropriate.

1.4 General Principles

1.4.1 One report for one active substance

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR,

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1 Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, Federal Register, 27 October 1994, pp. 54046-54064

2 International Reporting of Periodic Drug-Safety Update Summaries. Final Report of CIOMS Working Group II, CIOMS - Geneva 1992

separate presentations of data for different dosage forms, indications or populations (e.g. children vs adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

1.4.2 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorisation applications and renewals, as well as data on serious, unlisted ADRs (see below 1.4.5), which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions, may represent a significant hazard, and in that sense be a "safety issue". Although these types of cases should not be included with the usual ADR presentations (i.e., line-listings and summary tabulations), such findings should be discussed within the PSUR (see section 2.8), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g., population exposed, duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, such data should be included and discussed in the PSUR, even if it is known that it is included in another company's PSUR.

1.4.4 International birthdate and frequency of review and reporting

Each medicinal product should have as an International Birth Date (IBD), the date of the first marketing authorisation for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorisation for any of the various authorisations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cutoff for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorisations at different times in different countries; it is during this early period that harmonisation of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept six-monthly PSURs or PSURs based on multiples of six months. Therefore, preparation of PSURs for all regulatory authorities should be based on data sets of six months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial approval for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g., children vs adults; prescription to non-prescription status). The potential consequences for the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting.

The MAH should submit a PSUR within 60 days of the data lock point.

1.4.5 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet"(CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already **LISTED** or is still **UNLISTED,** terms which are introduced to distinguish them from the usual terminology of "expectedness" or "labeledness" which is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.

1.4.6 Presentation of data on individual case histories

Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

a) Direct reports to MAH (or under MAH control):

- Spontaneous notifications from health care professionals
- Spontaneous notifications from non-health care professionals or from consumers (non-medically substantiated)
- MAH-sponsored clinical studies* or named-patient ("compassionate") use

b) Literature

c) ADR reporting systems of regulatory authorities

d) Other sources of data:

- reports on ADRs exchanged between contractual partners (e.g., licensors-licensees)
- data in special registries, such as maintained in organ toxicity monitoring centres
- reports created by poison control centres
- epidemiologic data bases

Description of the reaction

Until an internationally agreed ICH coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company.

Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make it available on request, the "verbatim" information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable)
- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data
- if a MAH disagrees with a diagnosis that is provided by the notifying health care professional, it may indicate such disagreement within the line listing of cases (see below)

* What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

- MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH's medical interpretation (identified by asterisk or other means).

Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see 1.4.6a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see 1.4.6d) might not be (1) possible without standardisation of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non-serious listed ADRs). Details are set out in section 2.6.4.

2. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR)

The following sections are organised as a sample PSUR. In each of the sections, guidance is provided on what should be included.

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: *(PRODUCT)*

MAH's NAME AND ADDRESS *(Corporate headquarters or other company entity responsible for report preparation)*

PERIOD COVERED BY THIS REPORT: *(dates)*

INTERNATIONAL BIRTH DATE: Date *(Country of IBD)*

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

TABLE OF CONTENTS FOR MODEL PSUR

Introduction .....

Worldwide market authorisation status .....

Update of regulatory authority or MAH actions taken
for safety reasons .....

Changes to reference safety information .....

Patient exposure.....

Presentation of individual case histories .....

Studies .....

Other information .....

Overall safety evaluation .....

Conclusion .....

APPENDIX: COMPANY CORE DATA SHEET .....

2.1 INTRODUCTION

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see 1.4.6), the possibility of data duplication should be noted.

2.2 WORLDWIDE MARKET AUTHORISATION STATUS

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorisation, and subsequent renewal;
- any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
- treatment indications and special populations covered by the market authorisation, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of a licence application submission if related to safety or efficacy;
- dates of launch when known;
- trade name(s).

Typically, indications for use, populations treated (e.g., children vs adults) and dosage forms will be the same in many or even most countries where the product is authorised. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorisations. For multiple authorisations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorisation date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organised. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 UPDATE OF REGULATORY AUTHORITY OR MAH ACTIONS TAKEN FOR SAFETY REASONS

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:

- marketing authorisation withdrawal or suspension;
- failure to obtain a marketing authorisation renewal;
- restrictions on distribution;
- clinical trial suspension;
- dosage modification;
- changes in target population or indications;
- formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 CHANGES TO REFERENCE SAFETY INFORMATION

The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference document (CCDS) may contain more "listed" information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences for the overall safety evaluation and for the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

2.5 PATIENT EXPOSURE

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognised that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of

dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

2.6 PRESENTATION OF INDIVIDUAL CASE HISTORIES

2.6.1 General considerations

- Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.
- With regard to the literature, MAHs should monitor standard, recognised medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what "primary source" is given a case, if there is a publication, it should be noted and the literature citation given.

In some countries, there is no requirement to submit medically unconfirmed spontaneous reports that originate with consumers or other non-health care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
- all serious reactions, and non-serious unlisted reactions, from the literature;
- all serious reactions from regulatory authorities

Collection and reporting of non-serious, **listed** ADRs may not be required in all ICH countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that

have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

2.6.3 Presentation of the line listing

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g., weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organised (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number
- Country in which case occurred
- Source (e.g., clinical trial, literature, spontaneous, regulatory authority)
- Age and sex
- Daily dose of suspected drug (and, when relevant, dosage form or route)
- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
- Dates of treatment. If not available, best estimate of treatment duration.
- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See Section 1.4.6 for guidance.
- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, **listed**, spontaneously reported reactions (see also 2.6.2)

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from Other Sources (see 1.4.6c) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in the table(s) or as a narrative.

2.6.5 MAH's Analysis of Individual Case Histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (Section 2.9).

2.7 STUDIES

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

2.7.1. Newly analysed company-sponsored studies

All relevant studies containing important safety information and newly analysed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2. **Targeted new safety studies** planned, initiated or continuing during the reporting period

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described under 2.7.1.

2.7.3. Published safety studies

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarised and publication reference(s) given.

2.8 OTHER INFORMATION

2.8.1. Efficacy-Related Information

For a product used to treat serious or life threatening diseases, an unusual level of lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2. Late-Breaking Information

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 2.9).

2.9 OVERALL SAFETY EVALUATION

A concise analysis of the data presented, taking into account any late-breaking information (Section 2.8.2.), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- A change in characteristics of listed reactions, e.g. severity, outcome, target population
- Serious **unlisted** reactions, placing into perspective the cumulative reports
- Non-Serious **unlisted** reactions
- An increased reporting frequency of **listed** reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- drug interactions
- experience with overdose, deliberate or accidental, and its treatment
- drug abuse or misuse
- positive or negative experiences during pregnancy or lactation
- experience in special patient groups (e.g., children, elderly, organ impaired)
- effects of long-term treatment.

2.10 CONCLUSION

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

APPENDIX: COMPANY CORE DATA SHEET

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

3. GLOSSARY OF SPECIAL TERMS

Company Core Data Sheet (CCDS) - A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI) - All relevant safety information contained in the Company Core Data Sheet 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 purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date) - The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

International Birth Date (IBD) - The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.

Listed Adverse Drug Reaction - An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

Spontaneous Report or **Spontaneous Notification** - An unsolicited communication to a company, regulatory authority or other organisation that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organised data collection scheme.

Unlisted Adverse Drug Reaction - An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.

TABLE 1: EXAMPLE OF PRESENTATION OF WORLDWIDE MARKET AUTHORISATION STATUS

Country	Action-Date	Launch Date	Trade Name(s)	Comments
Sweden	A - 7/90 AR - 10/95	12/90 -	Bacteroff -	- -
Brazil	A - 10/91 A - 1/93	2/92 3/93	Bactoff Bactoff-IV	- IV dosage form
United Kingdom	AQ - 3/92 A - 4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (> 65) excluded (PK) Topical cream
Japan	LA - 12/92	-	-	To be refiled
France	V - 9/92	-	-	Unrelated to safety
Nigeria	A - 5/93 A - 9/93	7/93 1/94	Bactoff Bactoff	- New indication
Etc...				

Abbreviations for Action: A = authorised; AQ = authorised with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorisation renewal.

TABLE 2: PRESENTATION OF INDIVIDUAL CASE HISTORIES

(SEE 2.6.2 AND 2.6.4 FOR FULL EXPLANATION)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH			
• Spontaneous ADR reports*	S	-	+
	NS U	-	+
	NS L**	+	-
• MAH sponsored studies	SA	-	+
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
• Regulatory authorities	S	-	+
• Contractual partners	S	+	-
• Registries	S	+	-

*** *Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.*

** *Line listing should be provided as PSUR addendum only on request by regulatory authorities.*

S = serious; L = Listed; A = attributable to drug (by investigator or sponsor); NS = non-serious; U = Unlisted.

TABLE 3: (EXAMPLE OF SUMMARY TABULATION) #

NUMBER OF REPORTS BY TERM (SIGNS, SYMPTOMS AND DIAGNOSES) FROM SPONTANEOUS (MEDICALLY CONFIRMED), CLINICAL STUDY AND LITERATURE CASES: ALL SERIOUS REACTIONS

(An * indicates an unlisted term)

Body system/ ADR term	**Spontaneous/ Regulatory bodies**	**Clinical studies**	**Literature**
CNS			
hallucinations*	2	0	0
etc.			
etc.			
_____ Sub-total	_____	_____	_____
CV			
etc.			
etc.			
_____ Sub-total	_____	_____	_____
Etc...			
TOTAL			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g., x-spontaneous/regulatory y-clinical study, and z-literaure cases)

 # This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g., serious and non-serious in the same table or as separate tables, etc.)

Clinical Safety Data Management
Periodic Safety Update Reports for Marketed Drugs

ADDENDUM TO ICH TOPIC E 2 C

TRANSMISSION TO CPMP	September 2002
TRANSMISSION TO INTERESTED PARTIES	September 2002
DEADLINE FOR COMMENTS	December 2002
FINAL APPROVAL OF ADDENDUM BY CPMP	February 2003
DATE FOR COMING INTO OPERATION	August 2003

PART II
ADDENDUM TO ICH E2C
CLINICAL SAFETY DATA MANAGEMENT PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

Introduction

This addendum is intended to provide practical guidance for the preparation of the Periodic Safety Update Report (PSUR) as recommended in the ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, which achieved Step 4 in November 1996. That guideline has been implemented in some but not all ICH countries.

The PSUR is a practical and achievable mechanism for summarizing interval safety data, especially covering short periods (e.g., 6 months or 1 year), and for conducting an overall safety evaluation. It is a tool for Marketing Authorization Holders (MAHs) to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

PSURs are of value and importance to all parties in protecting the public health. The ICH E2C Guideline was developed to harmonize PSURs submitted to the Regulatory Authorities in terms of content and format as well to introduce the concept of International Birthdate (IBD). However, the original E2C Guideline has been interpreted in different ways by both MAHs and Regulatory Authorities. These differing interpretations have resulted in a perception that the guideline was not sufficient to accommodate the broad range of products and diverse circumstances that arise in practice. The Council for International Organizations of Medical Sciences (CIOMS) Working Group V1 made several recommendations and developed new concepts that harmonize the practice of preparing PSURs that have been taken into account in preparing this Addendum.

This Addendum addresses only those E2C provisions considered to need further clarification, guidance, or increased perceived flexibility beyond that provided in the ICH E2C guideline. This document should always be used in conjunction with the E2C Guideline.

This Addendum addresses the following concepts not previously addressed by E2C:

- Summary Bridging Report (see Section 1.4.4.2)
- Addendum Report (see Section 1.4.4.3)
- Proprietary information (see Section 2)
- Executive Summary (see Section 2)
- Risk management programme (see Section 2.8.3)
- Benefit-risk analysis (see Section 2.8.4)

To facilitate the use of this document, the numbering of the sections and paragraphs is identical to those of the E2C guideline.

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1 Report of CIOMS Working Group V: Current Challenges in Pharmacovigilance: Pragmatic Approaches. CIOMS, 2001, Geneva.

1.4. General Principles

1.4.1 One Report for One Active Substance

It is strongly recommended that information on all indications, dosage forms, and regimens for the active substance be included in a single PSUR, with a single data lock point common for all aspects of product use. There is a great advantage to having a consistent, broad-based examination of the safety information for the active substance(s) in a single document. When relevant, data relating to a particular indication, dosage form, or dosing regimen should be presented in a separate section within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

There are instances when separate PSURs might be considered appropriate. In these cases, the Regulatory Authorities should be notified and their agreement obtained at the time of authorization.

Examples include:

- Fixed combinations: Options include either a separate PSUR for the combination with cross-reference to the single agent(s) PSUR(s) or inclusion of the fixed combination data within one of the single agent PSURs.

- When an active substance is used in two or more different formulations (e.g., systemic preparations vs topical administration), two or more PSURs, with the same or different IBDs, can be useful.

1.4.4 International Birthdate and Frequency of Review and Reporting

Whenever possible, PSURs should be based on the IBD. If, in the transition period to a harmonized birthdate for that product, the use of a local approval date is appropriate, the MAH can submit its already prepared IBD-based PSUR plus:

- Line-listings and/or summary tabulations covering the additional period (when the additional period is less than 3 months for a 6 month or annual PSUR, or 6 months for a longer duration PSUR) with comment on whether the data reveal a new and important risk

or

- an Addendum Report when the additional period is greater than 3 months for a 6 month or an annual PSUR, or 6 months for a longer duration PSUR (see section 1.4.4.3)

1.4.4.1 Synchronization of National Birthdates with the IBD

For drugs that are on the market in many countries, the MAH can synchronize local or national birthdates with the IBD.

For a drug where the IBD is not known, the MAH can designate an IBD to allow synchronization of reports to all Regulatory Authorities. Once an IBD is designated, the MAH should notify the Regulatory Authorities, and the IBD should be adhered to thereafter.

It is recognized that long intervals between approvals could put the drug in a 5-year cycle in one region and a 6-month cycle in another region. For practical purposes, if a single month,

day and year for the IBD is not attainable, the MAH can contact the Regulatory Authorities to negotiate a mutually acceptable birth month and day. For example, where there are different approval dates, it can be useful for reports to be submitted on the same month and day (e.g., every January 18 and July 18), whether every 6 months, annually, or every 5th year.

1.4.4.2 Summary Bridging Reports

A Summary Bridging Report is intended to be a concise document integrating the information presented in two or more PSURs to cover a specified period over which a single report is requested or required by Regulatory Authorities. The report should not contain any new data but should provide a brief summary bridging two or more PSURs (e.g., 2 consecutive 6-month reports for an annual report or 10 consecutive 6-month reports to make a 5-year report). The Summary Bridging Report is intended to assist Regulatory Authorities with a helpful overview of the appended PSURs. The PSUR data should not be repeated but should be cross-referenced to individual PSURs. The format of the Summary Bridging Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers (see CIOMS V Report pp. 154-156). Upon request from the Regulatory Authority, a summary tabulation of serious, unlisted reactions should be included in the Summary Bridging Report.

Summary Bridging Reports can be used in situations where the MAH prepares short duration reports (e.g., 6-month or annual reports) indefinitely, especially if new indications or formulations are likely to be introduced over the years. For reports considered out of date relative to a particular Regulatory Authority's requirement, an Addendum Report could also be submitted (see Section 1.4.4.3). For a PSUR that spans longer time intervals, e.g., 5 years, an Addendum Report would only be considered appropriate if the time since preparation of the 5-year PSUR and the locally required report is greater than 6 months.

The Summary Bridging Report ordinarily should not include line listings. If summary tables covering the period of the appended PSURs are considered appropriate, there should be a clear understanding that the tables will be generated from live databases, which change over time as cases are updated. These tables will then reflect the most up-to-date data available at the time they are generated. It is recognized that the case counts in these summary tables can differ somewhat from the contents of the individual tables in the appended PSURs. A general statement describing the differences should be provided.

1.4.4.3 Addendum Reports

MAHs should set IBDs for all their products and can synchronize their local renewals. However, when a requested or required report covers data that fall outside the defined period, use of an Addendum Report is recommended.

An Addendum Report is an update to the most recently completed PSUR when a Regulatory Authority requests or requires a safety update outside the usual IBD reporting cycle. An Addendum Report should be used when more than 3 months for a 6-month or an annual report, and more than 6 months for a longer-interval report, have elapsed since the data lock point of the most recent PSUR. It might also be appropriate to provide an addendum to the Summary Bridging Report.

The Addendum Report should summarize the safety data received between the data lock point of the most recent PSUR and the Regulatory Authority's requested cut-off date. It is not intended that the Addendum Report provide an in-depth analysis of the additional cases, as these can be included in the next regularly scheduled PSUR. Depending on circumstances and the volume of additional data since the last scheduled report, an Addendum Report can

follow the ICH E2C format or a simplified presentation. The proposed minimal report should include the following sections containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

- Introduction (purpose; cross reference to most recent PSUR)
- Changes to the Company Core Safety Information (CCSI) 3 (including a copy of the most recent CCSI document if it differs from the one in the PSUR)
- Significant regulatory actions bearing on safety
- Line listing(s) and/or summary tabulations
- Conclusions (brief overview of new information and any impact on the known safety profile)

1.4.4.4 Restarting the Clock

For products in a long-term PSUR cycle, the return to 6-monthly or annual reporting could apply after important additions or changes in clinical use are first approved in an ICH region, such as:

- A new, clinically dissimilar indication
- A previously unapproved use in a special patient population, such as children, pregnant women or the elderly
- A new formulation or new route of administration

The decision on whether to restart the clock should be discussed with the Regulatory Authority no later than the time of granting the relevant marketing authorization.
Even if the clock "restarts," the analyses in the PSUR should focus on the newly-indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

1.4.4.5 Time Interval between the Data Lock Point and the Submission

In regions where they are required, PSURs are to be submitted within 60 days of the data lock point. To facilitate the preparation of both current and future PSURs, as well as safety reports outside of the PSUR, the RA will attempt to send comments to the MAH:

- as rapidly as possible, if any issues of non-compliance with the ICH format and content of a PSUR are identified (particularly those that preclude review)

- as rapidly as possible, if additional safety issues are identified that could prompt further evaluation by the MAH that should either be included in the next PSUR or provided as a separate stand-alone report

- before the next data lock point, if any additional analyses or issues of content are identified that should be included in the next PSUR.

Additional Time for Submissions

In rare circumstances, an MAH can make a special request to the Regulatory Authority for 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The RA will attempt to send response to MAH as rapidly as possible.

The basis of such a request should be justified and could include:

2 Report of CIOMS Working Group III and V, CIOMS, Geneva, 1999

- A large number of case reports for the reporting period, provided that there is no new significant safety concern

- Issues raised by Regulatory Authorities in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR

- Issues identified by the MAH for additional or further analysis

The MAH should make such a request only for the single PSUR in question and not for subsequent PSURs. The Regulatory Authority will generally expect subsequent PSURs to be submitted on the appropriate date and to retain their original periodicity.

1.4.5 Reference Safety Information

It is important to highlight the differences between the CCSI and the local product information/local labelling in the cover letter accompanying the local submission of the PSUR, as described in E2C section 2.4.

PSUR covering a period of 6 months or 1 year

For 6-month and annual reports, the version of the CCSI in effect at the beginning of the period covered by the report should be used as the reference.

PSUR covering a period of over 1 year

When producing a longer duration PSUR or a Summary Bridging Report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period. There can be considerable variation in listedness over the reporting period, depending on when the assessment of listedness is made (e.g., on an ongoing basis, such as at AE/ADR case entry, or when a PSUR is compiled). The latest CCSI in effect at the end of the period can be used. The MAH should ensure that all changes to the CCSI made over the period are described in Section 4 of the PSUR ("Changes to the Reference Safety Information").
When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text. MAHs assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any changes in listedness assessment over time. In both cases, changes made to the CCSI since the previous PSUR should be explained in Sections 4 ("Changes to Reference Safety Information") and/or 9 ("Overall Safety Evaluation").

2. Model For a Periodic Safety Update Report (PSUR)

PSURs contain proprietary information. Therefore, the Title page of a PSUR should contain a statement on the confidentiality of the data and conclusions included in the report.

MAHs should prepare a brief overview of each PSUR to provide the reader with a description of the most important information. This Executive Summary should be placed at the beginning of the PSUR immediately after the Title page. An example of an Executive Summary can be found in the CIOMS V report (pp. 333).

2.5 Patient Exposure

Estimations of patient exposure for marketed drugs often rely on gross approximations of in-house or purchased sales data or volume. This information is not always reliable or available for all products. For example, hospital-based (inpatient exposure) statistics from the major use-monitoring sources are frequently unavailable. It is also difficult to obtain accurate data for generics, non-prescription drugs, or multiple drug regimens. Background information, detailed explanation, and examples of patient exposure estimations are given in the CIOMS V report (pp. 167–181).

When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH can make extrapolations using the available data. When this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g., stable sales over a long period of time, seasonality of use of the product).

The MAH should use a consistent method of calculation across PSURs for the same product. If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PSUR introducing the change.

In Summary Bridging Reports, recalculation of patient exposure data to cover the entire reporting period can be appropriate if the exposure periods used in the individual PSURs overlap.

As described in E2C, when the pattern of reports indicate a potential safety problem, detailed presentation by clinical indication, approved or unapproved, should be provided when available.

2.6 Presentation of Individual Case Histories

There is no specific guidance in E2C on the presentation of individual case report narratives. As it is impractical to present all case reports for the reporting period in this section of the PSUR, a brief description of the criteria used to select cases for presentation should be given.

This section should contain a description and analysis of selected cases, including fatalities, presenting new and relevant safety information and grouped by medically relevant headings or System Organ Classes (SOCs).

2.6.1 General Considerations

Consumer and Other Non-healthcare Professional Reports

MAHs should prepare standard line listings and tabulations that are considered acceptable by all Regulatory Authorities, as described in E2C. To achieve this goal, MAHs should follow a consistent practice across all PSURs for all products by presenting consumer and other non-healthcare professional reports in separate line listings. When included in the analysis of safety issues in section 6 or 9, consumer reports should clearly be identified as such.

2.6.3 Presentation of the Line Listing

"Comments" field

E2C indicates that the "Comments" field should be used only for information that helps to clarify individual cases.

2.7 Studies

Only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information, should be included with a discussion of any final or interim results. The MAH should not routinely catalogue or describe all the studies.

2.8 Other Information

2.8.3 Risk Management Programmes

When an MAH has specific risk management programmes in place, they can be discussed in this Section.

2.8.4 Benefit-risk analysis report

When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this Section.

2.9 Overall Safety Evaluation

Discussion and analysis for the Overall Safety Evaluation should be organized by SOC rather than by listedness or seriousness. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.

ICH Topic E 2 D
Post Approval Safety Data Management

NOTE FOR GUIDANCE ON DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING
(CPMP/ICH/3945/03)

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CLINICAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

ICH Harmonised Tripartite Guideline

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1. INTRODUCTION

It is important to establish an internationally standardized procedure in order to improve the quality of post-approval safety information and to harmonise the way of gathering and

reporting information. The ICH E2A guideline provides guidance on pre-approval safety data management. Although many stakeholders have applied ICH E2A concepts to the post-approval phase, there is a need to provide further guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices. This guideline is based on the content of ICH E2A guideline, with consideration as to how the terms and definitions can be applied in the post-approval phase of the product life cycle.

2. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH POST-APPROVAL DRUG SAFETY EXPERIENCE

2.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

2.2. Adverse Drug Reaction (ADR)

Adverse drug reactions, as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline).

A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

2.3. Serious AE/ADR

In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

* results in death
* is life-threatening

  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
* requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
* results in persistent or significant disability/incapacity,
* is a congenital anomaly/birth defect,
* is a medically important event or reaction.

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

2.4. Unexpected ADR

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics) should be considered unexpected. When a Marketing Authorisation Holder (MAH) is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

"Class ADRs" should not automatically be considered to be expected for the subject drug. "Class ADRs" should be considered expected only if described as specifically occurring with the product in the local/regional product labeling. This is illustrated in the following examples:

- "As with other drugs of this class, the following undesirable effect occurs with Drug X."
- "Drugs of this class, including Drug X, can cause..."

If the ADR has not been documented with Drug X, statements such as the following are likely to appear in the local/regional product labeling:

- "Other drugs of this class are reported to cause…"
- "Drugs of this class are reported to cause..., but no reports have been received to date with Drug X."

In these situations, the ADR should not be considered as expected for Drug X.

NOTE: The term "listedness" is not applicable to expedited reporting but should be used to characterize the ADR according to the Company Core Safety Information (refer to ICH E2C guideline for definitions).

2.5. Healthcare Professional

Healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations.

2.6. Consumer

Consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, or relative of a patient.

3 Sources of Individual Case Safety Reports

3.1. Unsolicited Sources

3.1.1. Spontaneous Reports

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Center, Poison Control Center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Stimulated reporting can occur in certain situations, such as notification by a "Dear Healthcare Professional" letter, publication in the press, or questioning of healthcare professionals by company representatives. These reports should be considered spontaneous.

Consumer adverse reaction reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation". Regulatory Authorities might require medical confirmation for the purpose of expedited reporting**.** Emphasis should be placed on the quality of the report and not on its source. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained.

3.1.2. Literature

Each MAH is expected to regularly screen the worldwide scientific literature by accessing widely used systematic literature reviews or reference databases. The frequency of the literature searches should be according to local requirements or at least every two weeks. Cases of ADRs from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, might qualify for expedited reporting. A regulatory reporting form with relevant medical information should be provided for each identifiable patient. The publication reference(s) should be given as the report source; additionally a copy of the article might be requested by the local regulatory authority to accompany the report. All company offices are encouraged to be aware of publications in their local journals and to bring them to the attention of the company safety department as appropriate.

The regulatory reporting time clock starts as soon as the MAH has knowledge that the case meets minimum criteria for reportability.

If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although the report should indicate that the specific brand was not identified.

If multiple products are mentioned in the article, a report should be submitted only by the applicant whose product is suspected. The suspect product is that identified as such by the article's author.

3.1.3. Internet

MAHs should regularly screen websites under their management or responsibility for potential ADR case reports. MAHs are not expected to screen external websites for ADR information. However, if an MAH becomes aware of an adverse reaction on a website that it does not manage, the MAH should review the case and determine whether it should be reported.

MAHs should consider utilising their websites to facilitate ADR data collection, e.g., by providing ADR forms for reporting or by providing appropriate contact details for direct communication.

Unsolicited cases from the Internet should be handled as spontaneous reports. For the determination of reportability, the same criteria should be applied as for cases provided via other ways.

In relation to such cases from the Internet e.g. e-mail, identifiability of the reporter refers to the existence of a real person, i.e., it is possible to verify that the patient and the reporter exist.

3.1.4. Other Sources

If an MAH becomes aware of a case report from non-medical sources, e.g. the lay press or other media, it should be handled as a spontaneous report. For the determination of reportability, the same criteria should be applied as for other reports.

3.2. Solicited Sources

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. Adverse event reports obtained from any of these should not be considered spontaneous.

For the purposes of safety reporting, solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or an MAH. Further guidance on study-related issues, such as managing blinded therapy cases, can be found in the ICH E2A guideline.

3.3. Contractual Agreements

The marketing of many medicines increasingly takes place through contractual agreements between two or more companies, which may market same product in the same or different countries/region. Arrangements vary considerably with respect to inter-company communication and regulatory responsibilities. Overall, this can be a complex issue.

In such relationships, it is very important that explicit licensing/contractual agreements specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities. Safety personnel should be involved in development of any agreements from the beginning. Processes should be in place to avoid duplicate reporting to the regulatory authority, e.g. assigning responsibility to one company for literature screening.

Whatever the nature of the arrangement, the MAH is ultimately responsible for regulatory reporting. Therefore, every reasonable effort should be made between the contracting partners to minimize the data exchange period so as to promote compliance with MAH responsibilities.

3.4. Regulatory Authority Sources

Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are subject to expedited reporting to other authorities by each MAH. Re-submission of serious ADR cases without new information to the originating regulatory authority is not usually necessary, unless otherwise specified by local regulation.

4. STANDARDS FOR EXPEDITED REPORTING

4.1. What Should Be Reported?

4.1.1. Serious ADRs

Cases of adverse drug reactions that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected reactions in an expedited manner varies among countries. Non-serious adverse reactions, whether expected or not, would normally not be subject to expedited reporting.

For reports from studies and other solicited sources, all cases judged by either the reporting healthcare professional or the MAH as having a possible causal relationship to the medicinal product would qualify as ADRs. For purposes of reporting, spontaneous reports associated with approved drugs imply a suspected causal relationship.

4.1.2. Other Observations

In addition to single case reports, any safety information from other observations that could change the risk-benefit evaluation for the product should be communicated as soon as possible to the regulatory authorities in accordance with local regulation. Examples include any significant unanticipated safety findings from an in vitro, animal, epidemiological, or clinical study that suggest a significant human risk, such as evidence of mutagenicity, teratogenicity, carcinogenicity, or lack of efficacy with a drug used in treating a life-threatening or serious disease.

4.1.2.1. Lack of Efficacy

Evidence of lack of efficacy should not normally be expedited, but should be discussed in the relevant periodic safety update report. However, in certain circumstances and in some regions, individual reports of lack of efficacy are considered subject to expedited reporting. Medicinal products used for the treatment of life-threatening or serious diseases, vaccines, and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered for expedited reporting. Clinical judgment should be used in reporting, with consideration of the local product labeling and disease being treated.

4.1.2.2. Overdose

Reports of overdose with no associated adverse outcome should not be reported as adverse reactions. Cases associated with serious adverse reactions are considered subject to expedited reporting, unless otherwise specified by local regulation. They should be routinely followed up to ensure that the information is as complete as possible with regard to symptoms, treatment, and outcome. The MAH should collect any available information on overdose related to its products.

4.2. Minimum Criteria for Reporting

It is recommended that as much information as possible be collected at the time of the initial report. However, for the purpose of regulatory reporting, the minimum data elements for an ADR case are: an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four elements means that the case is considered incomplete; however, MAHs are expected to exercise due diligence to collect the missing data elements.

4.3. Reporting Time Frames

In general, expedited reporting of serious and unexpected ADRs is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH. Time frames for other types of serious reports vary among countries, depending on source, expectedness and outcome.

The regulatory reporting time clock is considered to start on the date when any personnel of the MAH first receive a case report that fulfills minimum criteria as well as the criteria for expedited reporting. In general, this date should be considered day 0.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited

reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

4.4. Non-serious ADRs

Cases of non-serious ADRs, whether expected or not, would not normally be considered reportable on an expedited basis. Non-serious ADRs should be included in the periodic safety update report according to the ICH E2C guideline.

5. GOOD CASE MANAGEMENT PRACTICES

Accurate, complete, and bona fide information is very important for MAHs and regulatory agencies identifying and assessing ADR reports. Both are faced with the task of acquiring sufficient information to help ensure that the reports are authentic, accurate, as complete as possible, and non-duplicative.

5.1. Assessing Patient and Reporter Identifiability[1]

Patient and reporter identifiability is important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases. The term identifiable in this context refers to the verification of the existence of a patient and a reporter.

Local data privacy laws regarding patient and reporter identifiability might apply.

One or more of the following should automatically qualify a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter.

All parties supplying case information or approached for case information should be identifiable: not only the initial reporter (the initial contact for the case), but also others supplying information.

In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "Two patients experienced…" or " a few patients experienced" should be followed up for patient-identifiable information before regulatory reporting.

5.2. The Role of Narratives

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, and ADR(s) including the outcome, laboratory evidence (including normal ranges), and any other information that supports or refutes an ADR. The narrative should serve as a comprehensive, stand-alone "medical story". The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient's experience, rather than in the chronology in which the information was received. In follow-up reports, new information should be clearly identified.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records should be included in the report, and their availability should be mentioned in the narrative and supplied on request. Any relevant autopsy or post-mortem findings should also be summarized in the narrative and related documents should be provided according to local regulation and if allowed by local data privacy laws.

Terms (e.g., AEs/ADRs, indication, and medical conditions) in the narrative should be accurately reflected in appropriate data fields.

5.3. Clinical Case Evaluation

The purpose of careful medical review is to ensure correct interpretation of medical information. Preferably, information about the case should be collected from the healthcare professionals who are directly involved in the patient's care. Regardless of the source of an ADR report, the recipient should carefully review the report for the quality and completeness of the medical information. The review should include, but is not limited to, the following considerations:

- Is a diagnosis possible?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- What additional information is needed?

ADR terms should be used consistently and in accordance with recommended standards for diagnosis, if possible. The report should include the verbatim term as used by the reporter, or an accurate translation of it. Any company personnel receiving reports should provide an unbiased and unfiltered report of the information from the reporter. While the report recipient is encouraged to actively query the reporter to elicit the most complete account possible, inferences and imputations should be avoided in report submission. However, clearly identified evaluations by the MAH are considered appropriate and are required by some regulatory authorities.

When a case is reported by a consumer, his/her description of the event should be retained, although confirmatory or additional information from any relevant healthcare professionals should also be sought and included.

5.4. Follow-up Information

The information from ADR cases when first received is generally incomplete. Ideally, comprehensive information would be available on all cases, but in practice efforts should be made to seek additional information on selected reports, including second –hand reports (see Attachment, Recommended Key Data Elements, of this guideline).

In any scheme to optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. The priority for follow-up should be as follows: cases which are 1) serious and unexpected, 2) serious and expected, and 3) non-serious and unexpected. In addition to seriousness and expectedness as criteria, cases "of special interest" also deserve extra attention as a high priority (e.g., ADRs under active surveillance at the request of the regulators), as well as any cases that might lead to a labeling change decision.

Follow-up information should be obtained, via a telephone call and/or site visit and/or a written request. The company should provide specific questions it would like to have answered. Follow-up methods should be tailored towards optimizing the collection of missing information. Written confirmation of details given verbally should be obtained whenever possible. In exceptional circumstances, if requests for information have been refused by the reporter, a regulatory authority might be able to assist an MAH in obtaining follow-up data.

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire/specific form is encouraged, preferably at the time of the initial report. Ideally,

healthcare professionals with thorough pharmacovigilance training and therapeutic expertise should be involved in the collection and the direct follow-up of reported cases (particularly those of medical significance). For serious ADRs, it is important to continue follow-up and report new information until the outcome has been established or the condition is stabilized. How long to follow up such cases is a matter of judgment.

It is important that at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable future investigations, within the constraints imposed by local data privacy laws.

5.4.1. Pregnancy Exposure

MAHs are expected to follow up all pregnancy reports from healthcare professionals or consumers where the embryo/foetus could have been exposed to one of its medicinal products. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (e.g., if medicinal products taken before the gestational period should be considered).

5.5. How to Report

The CIOMS I form has been a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain basic information/data elements, when available, be included with any expedited report, whether in a tabular or narrative presentation. It is recommended that the Medical Dictionary for Regulatory Activities (MedDRA) be used for coding medical information. The standards for electronic submission of Individual Case Safety Reports (ICSRs), according to the ICH E2B/M2 guidelines, should be implemented.

The listing in the Attachment of this guideline addresses those data elements regarded as desirable; if all relevant elements are not available at the time of expedited reporting, efforts should be made to obtain them.

Attachment

RECOMMENDED KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

Some data elements might not be relevant, depending on the circumstances. Attempts should be made to obtain follow-up information on as many other listed items as are pertinent to the case. Refer to the ICH E2B/M2 guidelines for detailed data elements for electronic transmission of ICSRs.

1. Patient Details

- Initials
- Other relevant identifier (patient number, for example)
- Gender
- Age, age category (e.g., adolescent, adult, elderly), or date of birth
- Concomitant conditions
- Medical history
- Relevant family history

2. Suspected Medicinal Product(s)

- Brand name as reported
- International Non-Proprietary Name (INN)
- Batch/lot number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose (specify units - e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, or duration of treatment

3. Other Treatment(s)

The same information as in item 2 should be provided for the following:

- Concomitant medicinal products
  (including non-prescription, over-the-counter medicinal products, herbal remedies, dietary supplements, complementary and alternative therapies, etc.) .
- Relevant medical devices

4. Details (all available) of Adverse Drug Reaction(s)

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious
- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, out-patient clinic, home, nursing home)
- Outcome (recovery and any sequelae)
- For a fatal outcome, stated cause of death

- Relevant autopsy or post-mortem findings
- Relatedness of product to reaction(s)/event(s)

5. Details on Reporter of an ADR

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, healthcare professional, etc.)
- Profession (specialty)

6. Administrative and MAH Details

- Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
- Date the event report was first received by manufacturer/company
- Country in which the event occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to authorities
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- Identifying regulatory code or number for marketing authorisation dossier
- Company/manufacturer's identification number for the case (the same number should be used for the initial and follow-up reports on the same case).

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACOVIGILANCE PLANNING

E2E

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E2E
Document History

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Current *Step 4* version

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PHARMACOVIGILANCE PLANNING

ICH Harmonised Tripartite Guideline

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HARMACOVIGILANCE PLANNING

1. INTRODUCTION

1.1 Objective

This guideline is intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug (in this guideline, the term "drug" denotes chemical entities, biotechnology-derived products, and vaccines). The main focus of this guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The guideline can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the Safety Specification and Pharmacovigilance Plan into the Common Technical Document (CTD).

The guideline describes a method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and conduct of observational studies. It does not describe other methods to reduce risks from drugs, such as risk communication. The guideline takes into consideration ongoing work in the three regions and beyond on these issues.

This guideline does not cover the entire scope of pharmacovigilance. It uses the WHO definition of the term 'pharmacovigilance' as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems." This definition encompasses the use of pharmacoepidemiological studies.

1.2 Background

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early postmarketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. This ICH guideline has been developed to encourage harmonisation and consistency, to prevent duplication of effort, and could be of benefit to public health programs throughout the world as they consider new drugs in their countries.

1.3 Scope

The guideline could be most useful for new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnologically-derived product) and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen.

The purpose of this guideline is to propose a structure for a Pharmacovigilance Plan, and a Safety Specification that summarises the identified and potential risks of the product to be addressed in the Plan. The guideline is divided into the following sections:

- Safety Specification;
- Pharmacovigilance Plan;
- Annex – Pharmacovigilance Methods.

It is recommended that company pharmacovigilance experts get involved early in product development. Planning and dialogue with regulators should also start long before license application. A Safety Specification and Pharmacovigilance Plan can also be developed for products already on the market (e.g., new indication or major new safety concern). The Plan could be used as the basis for discussion of pharmacovigilance activities with regulators in the different ICH regions and beyond.

For products with important identified risks, important potential risks or important missing information, the Pharmacovigilance Plan should include additional actions designed to address these concerns. For products for which no special concerns have arisen, routine pharmacovigilance as described in section 3.1.2 should be sufficient for post-approval safety monitoring, without the need for additional actions (e.g., safety studies).

During the course of implementing the various components of the Plan, any important emerging benefit or risk information should be discussed and used to revise the Plan.

The following principles underpin this guideline:

- Planning of pharmacovigilance activities throughout the product life-cycle;
- Science-based approach to risk documentation;
- Effective collaboration between regulators and industry;
- Applicability of the Pharmacovigilance Plan across the three ICH regions.

2. SAFETY SPECIFICATION

The Safety Specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period. This Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan. The Safety Specification can be built initially during the pre-marketing phase and, at the time

approval is sought, it should reflect the status of issues that were being followed during development.

The Common Technical Document (CTD), especially the Overview of Safety [2.5.5], Benefits and Risks Conclusions [2.5.6], and the Summary of Clinical Safety [2.7.4] sections, includes information relating to the safety of the product, and should be the basis of the safety issues identified in the Safety Specification. Sponsors should support the Safety Specification with references to specific pages of the CTD or other relevant documents. The Safety Specification can be a stand-alone document, usually in conjunction with the Pharmacovigilance Plan, but elements can also be incorporated into the CTD. The length of the document will generally depend on the product and its development program. Appendices can be added if it is considered important to provide a more detailed explanation of important risks or analyses.

2.1 Elements of the Specification

It is recommended that sponsors follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included are only a guide. The Safety Specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

The focus of the Safety Specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.

2.1.1 Non-Clinical

Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.);
- Drug interactions;
- Other toxicity-related information or data.

If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

2.1.2 Clinical

a. Limitations of the Human Safety Database

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The world-wide experience should be briefly discussed, including:

- The extent of the world-wide exposure;
- Any new or different safety issues identified;
- Any regulatory actions related to safety.

b. Populations not Studied in the Pre-Approval Phase

The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5). Populations to be considered should include (but might not be limited to):

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

c. Adverse Events (AEs) / Adverse Drug Reactions (ADRs)

This section should list the important identified and potential risks that require further characterisation or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented (e.g., relevant sections of the CTD 2.5.5 and 2.7.4).

Discussion of risk factors and potential mechanisms that apply to identified AEs/ADRs should draw on information from any part of the CTD (non-clinical and clinical) and other relevant information, such as other drug labels, scientific literature, and post-marketing experience.

Identified risks that require further evaluation

More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.).

Potential risks that require further evaluation

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association.

d. Identified and Potential Interactions, Including Food-Drug and Drug-Drug Interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

e. Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates). For example, if condition X is an important adverse event in patients who are treated with drug Y for disease Z, then it is useful to review the incidence of condition X in patients with disease Z who are not treated with drug Y; this is the background rate of condition X among patients with disease Z. Information on risk factors for an adverse event (condition X) would also be useful to include, if available.

f. Pharmacological Class Effects

The Safety Specification should identify risks believed to be common to the pharmacological class.

2.2 Summary

At the end of the Safety Specification a summary should be provided of the:

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

Sponsors are encouraged to summarise specific ongoing safety issues on an issue-by-issue basis, including both non-clinical and clinical data that are pertinent to the problem.

3. PHARMACOVIGILANCE PLAN

This section gives guidance on the structure of a Pharmacovigilance Plan. The Pharmacovigilance Plan should be based on the Safety Specification. The Specification and Plan can be written as two parts of the same document. The Plan would normally be developed by the sponsor and can be discussed with regulators during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises post-marketing. It can be a stand-alone document but elements could also be incorporated into the CTD.

For products for which no special concerns have arisen, routine pharmacovigilance as described in section 3.1.2 should be sufficient for post-approval safety monitoring,

without the need for additional actions (e.g., safety studies). However, for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

The length of the document will likely depend on the product and its development program. The Pharmacovigilance Plan should be updated as important information on safety becomes available and milestones are reached.

3.1 Structure of the Pharmacovigilance Plan

Outlined below is a suggested structure for the Pharmacovigilance Plan. The structure can be varied depending on the product in question and the issues identified in the Safety Specification.

3.1.1 Summary of Ongoing Safety Issues

At the beginning of the Pharmacovigilance Plan a summary should be provided of the:

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

This is important if the Pharmacovigilance Plan is a separate document from the Safety Specification.

3.1.2 Routine Pharmacovigilance Practices

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a Pharmacovigilance Plan. This routine pharmacovigilance should include the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- The preparation of reports for regulatory authorities:
    - Expedited adverse drug reaction (ADR) reports;
    - Periodic Safety Update Reports (PSURs).
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities;
- Other requirements, as defined by local regulations.

In some ICH regions, there might be a regulatory requirement to present within the Pharmacovigilance Plan an overview of the company's organisation and practices for conducting pharmacovigilance. In the absence of such a requirement, a statement that the company's routine pharmacovigilance practices include the elements outlined in the bulleted list above should be sufficient.

3.1.3 Action Plan for Safety Issues

The Plan for each important safety issue should be presented and justified according to the following structure:

- Safety issue;
- Objective of proposed action(s);
- Action(s) proposed;
- Rationale for proposed action(s);
- Monitoring by the sponsor for safety issue and proposed action(s);
- Milestones for evaluation and reporting.

Any protocols for specific studies can be provided in the CTD section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., Module 4 if the study is a non-clinical study).

3.1.4 Summary of Actions to be Completed, Including Milestones

An overall Pharmacovigilance Plan for the product bringing together the actions for all individual safety issues should be presented. Whereas section 3.1.3 suggests presenting an action plan by ongoing safety issue, for this section the Pharmacovigilance Plan for the product should be organised in terms of the actions to be undertaken and their milestones. The reason for this is that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified issues.

It is recommended that milestones for completion of studies and other evaluations, and for submission of safety results, be included in the Pharmacovigilance Plan. In developing these milestones one should consider when:

- Exposure to the product will have reached a level sufficient to allow potential identification/characterisation of the AEs/ADRs of concern or resolution of a particular concern; and/or
- The results of ongoing or proposed safety studies are expected to be available.

These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment and license renewals) and used to revise the Pharmacovigilance Plan.

3.2 Pharmacovigilance Methods

The best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most appropriate design. The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid sponsors considering possible methods to address specific issues identified by the Safety Specification. This list is not all-inclusive, and sponsors should use the most up-to-date methods that are relevant and applicable.

3.2.1 Design and Conduct of Observational Studies

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non-interventional, non-experimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator "observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice."[1]

Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalised. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan.

Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings.

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.[2] In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed.

ANNEX - Pharmacovigilance Methods

1. Passive Surveillance

- Spontaneous Reports

  A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organisation (e.g., WHO, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme.[1]

  Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.[2,3,4,5]

  Systematic Methods for the Evaluation of Spontaneous Reports

  More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection[6,7,8]. Data mining techniques have also been used to examine drug-drug interactions[9]. Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognising the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

- Case Series

  Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are

certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome[10,11]. Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

2. Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods[12]. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early post-marketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

3. Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact[13]. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

- Sentinel Sites

  Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites[14]. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, haemodialysis centres, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain

clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

- Drug Event Monitoring

  Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire[12,15,16,17]. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

- Registries

  A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardised questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

  Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

4. Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective)[12,15].

- Cross-Sectional Study (Survey)

  Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilised when exposures do not change over time.

- Case-Control Study

  In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction, that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

- Cohort Study

  In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates

can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

There are several automated databases available for pharmacoepidemiologic studies[12,15,18]. They include databases which contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

5. Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolise drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the

event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

6. Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

- Natural History of Disease

  The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective[15]. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

- Drug Utilisation Study

  Drug utilisation studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes[12]. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product

Question Bank

1. Explain the Definitions and Standards for Expedited Reporting?
2. Describe Periodic Safety Update Reports for Marketed Drugs.
3. Explain Post Approval Safety Management.
4. Discuss on Pharmacovigilance Planning.

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UNIT – III - Pharmacovigilance regulations and guidelines – SMB5401

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COURSE MATERIAL

Subject Name: Pharmacovigilance and Safety monitoring **Subject Code: SMB5401**

UNIT – III

Role of Pharmacovigilance in Drug Regulation

Drug regulatory arrangements provide the foundation for a national ethos of drug safety, and for public confidence in medicines. The issues with which drug regulatory authorities have to contend besides the approval of new medicines, include:

- Clinical trials
- Safety of complementary and traditional medicines, vaccines and biological medicines
- Developing lines of communication between all parties with an interest in drug safety and ensuring that they are open and able to function efficiently, particularly at times of crisis.

Pharmacovigilance programmes need strong links with regulators to ensure that authorities are well briefed on safety issues in everyday practice that may be relevant to future regulatory action. Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products. Pharmacovigilance programmes need to be adequately supported to achieve their objectives.

Introduction

A new medicine must pass three hurdles before its approval by the national drug regulatory authority.

Sufficient evidence is required to show the new drug to be

- of good quality,
- effective, and
- safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval, the issue of safety is less certain. Safety is not absolute, and it can be judged only in relation to efficacy, requiring judgement on the part of the regulators in deciding on acceptable limits of safety.

There is a possibility that rare yet serious adverse events (such as those occurring with a frequency of, say, one in five thousand) will not be detected in the pre-registration development of the drug. For example, fatal blood dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be recognized after 15,000 patients have been treated and observed, provided that the background incidence of such a reaction is zero or a causal association with the drug is clear.

This arbitrary 'rule of three' is based on the experience that for any given adverse effect approximately threefold the number of patients need to be treated and observed for the side effect to become manifest and reliably linked with the drug assuming a background incidence of zero of the effect being observed.

Clinical trial regulation

In recent years there has been a substantial increase in the number of clinical trials in developed and developing countries. Clinical trials in the United States of America alone nearly doubled between 1990 and 1998. With sequencing of the human genome, clinical research in potential new drug therapies is likely to increase even further.

There is also a growing alliance between academia and the pharmaceutical and biotechnology industries. This has given rise to serious and widespread concern over ethical and scientific issues such as:

- the potential for conflict of interest
- unethical patient recruitment practices
- inadequacy of informed consent
- lack of capacity to ensure on-going monitoring of clinical trials and adherence to principles of sound and ethical clinical practice
- poor reporting and management of adverse events.

For drug regulators, the changing trends over recent years in the conduct of clinical trials present special and urgent challenges, particularly in ensuring that the rights and health of patients and their communities are protected. In their approval of clinical trials, regulatory bodies look at safety and efficacy of new products under investigation. They must also pay attention to the general standards of care and safety of study subjects, in conjunction with the appropriate institutional review boards (IRBs).

Medicines that are required for diseases such as tuberculosis, malaria, HIV/AIDS and meningococcus A meningitis, and those which may have a questionable or uncertain effectiveness - safety profile, require careful surveillance when first introduced on a large scale into communities.

The increasing complexity of clinical trials presents further challenges to regulators. Study designs often require large cohorts of participants. In many instances trials are carried out at various sites in several

countries. Local ethics committees and drug regulators are not always aware of patients' and investigators' experiences at other international sites. Clinical trials are increasingly contracted to clinical research organizations and patient recruitment agencies, which act as intermediaries between the sponsors of the study, the investigators and the patients.
Responsibility for ensuring proper conduct of the clinical trial may, in such circumstances, be divided between the parties. Information requested by ethics committees and regulators may be difficult to obtain in a short time. Regulators and ethics committees do not always have the capacity to carry out these functions effectively. This may have serious implications for the safety of patients.

Safety monitoring during clinical trials is now recognized as one of the major concerns for new drug development. This is currently being addressed by a CIOMS working group. Three main topics are being addressed:

1) the collection of adverse experience information
2) assessment/monitoring of clinical data
3) reporting/communication of clinical data.

A standardized reporting system for safety concerns arising during clinical trials might serve as a helpful tool for regulatory agencies, and for ethics committees (institutional review boards), provided there were full exchange of information between them and the investigators and sponsors. Expedited electronic submission of safety reports in ICH countries has facilitated the reporting process to some extent; however, routine review of safety information requires considerable resources, expertise, support and commitment from those involved.

Once research into new drugs is in the post-marketing stage (Phase IV studies) safety may be monitored to comply with the conditions of registration, particularly when there are unresolved concerns. This may lead to improved and more rapid changes in labelling or even withdrawal of a new drug from the market. Routine application of principles of good clinical practice that ensure patient safety and strict compliance with prescribed regulatory requirements would substantially improve standards of clinical trials.

Post-marketing safety monitoring

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing (approval) phase, if important innovations are not to be lost in an unduly restrictive regulatory net. Judgement as to whether and how this might happen lies with the regulators.

The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that there should be detailed pharmacovigilance in the early years after a drug's release.

Careful safety monitoring is not confined, however, to new drugs or to significant therapeutic advances. It has an important role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available, where new safety issues may have arisen. In a developing country, these latter considerations are likely to be more important than the benefits a novel therapeutic entity might bring to an already pressed health service.

While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a comparator.[26] More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions. They need to be incorporated into post-marketing surveillance programmes. There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines. These include:

- detection of drug interactions
- measuring the environmental burden of medicines used in large populations
- assessing the contribution of 'inactive' ingredients (excipients) to the safety profile
- systems for comparing safety profiles of similar medicines
- surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

A more difficult question is whether pharmacovigilance has resulted in inappropriate removal from the market of potentially useful medicines as a result of misplaced fears or false signals.

The CIOMS report on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines. Systematic medical and

prescription record linkage, with drug utilization studies, would contribute to greater accuracy. This is a responsibility that falls outside the strict traditional terms of reference of national pharmacovigilance centres.

Promotional activities

The safety of medicines in the development stage is increasingly affected by the constraints placed by sponsors on the study plan, laboratory programme and the open sharing of information as the research agenda is negotiated with clinical collaborators. There is growing public concerns that close collaboration between academia and the pharmaceutical industry may adversely affect medical practice and clinical research.

A worrying development for drug safety is 'direct to consumer' advertizing by pharmaceutical manufacturers, other sellers of medicines and parties with a vested interest. Spending on this activity has doubled in the USA over the past four years. While it may improve patients' understanding and is in keeping with the need to improve access to drug information, lack of reliability and accuracy may compromise patient care and safety.

Even where direct advertizing of prescription medicines to consumers is illegal, the Internet provides a medium that makes communication possible across borders. This may make national regulations about advertizing ineffective. Websites now make it possible to buy and sell prescription drugs such as benzodiazepines without controls. These developments in communication all have an impact on the safety of medicine.

All these issues suggest the need for more thorough monitoring of drug safety and scrutiny of advertizing. Resources and expertise are necessary to ensure that promotional materials contain accurate and balanced information, and that practices are ethical. Self-regulation by industry is unlikely to be sufficient in many countries. Regional or international collaboration in the implementation of a regulatory code of practice for advertizing medicinal products, overseen by an impartial advisory body, would help in this regard. Misrepresentation and lack of full disclosure may have equally important and potentially serious safety implications. Certain international medical journals have developed a uniform policy that reserves the right to refuse to publish drug company-sponsored studies unless the researchers are guaranteed scientific independence. A joint editorial, which outlines the rationale for this policy, states that this action is a response to the industry's increasingly tight control over research, results and, in many cases, whether and how results are made public.[33] More collaboration with journalists and the media needs to be fostered to ensure the objectivity and reliability of published medical information.

Regulatory aspects in Pharmacovigilance

History:

In 1986, India proposed Adverse Drug Reaction Monitoring System (ADR monitoring System). It had 12 regional centers. India joined World Health Organization WHO-ADR Monitoring Programme in1998. In 2004-08, India had started National Pharmacovigilance Programme which was performing under 2 Zonal, 5 regional and 24 Peripheral Regions.

Currently India is having Pharmacovigilance Programme of India which has commenced from 2010. Pharmacovigilance Programme of India (PvPI): It is 5 year programmed and it comprises of 5 phases:-

- Initial Phase (2010-11),
- Expansion and Consolidation phase (2011-12),
- Expansion and maintenance phase (2012-13),
- Expansion and optimization phase (2013-14)
- The Excellence Phase (2014-15).

Scope:

Due to considerable social and economic consequences of adverse drug reactions there is a need to engage health-care professionals and the public at huge, in a well-structured programme to build collaborations for monitoring adverse drug reactions.

Purpose:

The purpose of the programme is to assemble data, examine it and use the inferences to recommend informed regulatory interventions, besides interconnecting risks to healthcare professionals and the public.

The Pharmacovigilance Programme has the following signposts:

- To nurture a culture of notification,
- To engross several healthcare professionals and NGOs in the drug monitoring and information distribution processes,
- To achieve such operational efficiencies that would make Indian Pharmacovigilance Programme a benchmark for global drug monitoring endeavors.

Regulations:

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in partnership with Indian Pharmacopeia commission, Ghaziabad has initiated a nation-wide Pharmacovigilance Programme for

protecting the health of the patients by guaranteeing drug safety. The Programme is being coordinated by the Indian Pharmacopeia commission, Ghaziabad works as a National Coordinating Centre (NCC). The centre operates under the supervision of a Steering Committee. The programme is coordinated by the National Pharmacovigilance Centre (NPC) at CDSCO. The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee (NPAC) to recommend procedures and guidelines for regulatory interventions. The Pharmacovigilance programme of India encourages reporting all the suspected adverse reaction related to drug which also includes of those suspected to have been caused by herbal, traditional or alternative remedies. Any health care professionals (Doctors including Dentists, Nurses, and Pharmacists) may report suspected adverse drug events. Suspected adverse drug events are report through ADR reporting form. After completion the form shall be returned/ forwarded to the same Pharmacovigilance Centre from where it was received.

ADR Reporting Procedure of India:

In India Reporting of ADR is done through following three ways under PvPI:

- Healthcare Professional;
- Consumer Reporting;
- Public Health Programme-PHP.

The reports are recorded through ADR reporting form by ADR monitoring centre /National Co-ordination Centre. Then they are entered into the vigiflow software and reports re-checked for it completeness. The access of report in vigiflow creates WORLWIDE UNIQE NUMBER.AMC personnel ensure the completeness and quality of the report and Causality assessment done by Centre Co-ordinator/Deputy Co-ordinator. Technical assessment is performed and follow-up is also done. Hard copy as well as soft copy is preserved and their access is restricted.

<u>European Union PV guidelines and Good Pharmacovigilance practices (GPP)</u>

Good pharmacovigilance practice (GVP) Modules:

I Pharmacovigilance systems and their quality systems

II Pharmacovigilance system master file

III Pharmacovigilance inspections

IV Pharmacovigilance audits

V Risk management systems

VI Management and reporting of adverse reactions to medicinal products

VII Periodic safety update report

VIII Post-authorisation safety studies

IX Signal management

X Additional monitoring

XV Safety communication

XVI Risk minimisation measures – selection of tools and effectiveness indicators

European Union PV guidelines

Background to Guidelines on good pharmacovigilance practices (GVP)GVP

New legislation for pharmacovigilance applies in the European Union (EU) since July 2012, and to support its implementation, a set of guidelines for the conduct of pharmacovigilance in the EU has been developed which, as they have been adopted, replaced the previous set in Volume 9A of the Rules Governing Medicinal Products in the EU.

This new guidance on good pharmacovigilance practices (GVP) is organised into two types of chapters, namely Modules on pharmacovigilance processes and Product- or Population-Specific Considerations.

History of the GVP development process and latest updates

The first seven Modules on prioritised processes were consulted between 21 February and 18 April 2012 and revised, taking into account the comments received from stakeholders. They were available in their first final versions which came into force on 2 July 2012.

Module III on pharmacovigilance inspections and Module X on processes for additional monitoring of medicinal products were released on 27 June 2012 for public consultation until 24 August 2012, and Module IV on pharmacovigilance audits and Module XV on safety communication were released on 26 July 2012 for public consultation until 21 September 2012. Modules III and IV were published in their final versions, together with the updated GVP Annex I on definitions, on 13 December 2012. The final Module XV was published on 24 January 2013, together with a Template for Direct Healthcare Professional Letters in the GVP Annex II. On 25 April 2013, the final Module X on additional monitoring was published as final, taking into account latest additional legislation.

Since their first release as final, some Modules have been revised as final, and further Modules and

Product- or Population-Specific Considerations chapters have been issued:

Module II was published in its first revision, mainly to provide clarifications for herbal medicinal products, on 12 April 2013. Module VIII Revision 1 and its Addendum Revision 1 as well as in Annex II
– Template for the PSUR Cover Page Revision 1 were published on 25 April 2013.

On 7 June 2013, the draft revision 1 of Module VI on the management and reporting of adverse reactions was released for public consultation, in order to provide more guidance on the clock state for reporting of valid case reports, reporting from post-authorisation safety studies as well as the handling of languages. Also on 7 June 2013, draft Module XVI on risk minimisation measures was released for public consultation. Both consultations closed on 5 August 2013. Module XVI was published in its final version on 28 February 2014; and revision 1 of Module VI was published as final on 15 September 2014.

The first chapter with Product- or Population-Specific Considerations, i.e. the chapter P.I on vaccines, was provided in its final version on 12 December 2013, following its public consultation launched on 12 April 2013. Also on 12 December 2013, revision 1 of Module VII on periodic safety update reports was provided in its final version following public consultation launched on 25 April 2013. This revision included updates for consistency with the recently finalised ICH-E2C(R2) guideline and on the operations in the EU.

The definitions relating to vaccine pharmacovigilance, launched for public consultation on 12 April 2013, were published on 8 January 2014 without any change post-consultation, together with other amendments to definitions and explanatory notes as detailed on page 2 of the GVP Annex I on definitions in its revision 2.

On 25 April 2014, revision 1 of Module V on risk management system was published, mainly to amend the requirements of part VI of the RMP as published already in the updated RMP templates, to introduce amendments in line with the new requirements for variation applications and to align the definitions of Missing information and Safety concern and their explanatory notes with legal requirements, as well as to amend the definition for Risk minimisation activity. Annex I on definitions was updated accordingly and published as revision 3, and likewise Module XVI on risk minimisation measures was published as revision 1.

On 15 September 2014, revision 1 of Module III was published with a reference to the new Union procedures for pharmacovigilance inspections.

On 27 April 2015, Addendum I to Module XVI on educational materials was published as a draft for

public consultation, and published as final on 15 December 2015.

On 11 August 2015, revision 1 of the Module IV was published with a clarifying note what does not constitute an audit, and a public consultation was launched for revision 2 of Module VIII and its Addendum, in particular to clarify the link between the legislation on non-interventional post-authorisation safety studies (PASS) and categories 1-4 of non-interventional PASS for risk management planning and to update procedural and transmission requirements. These documents, having been amended in the light of their public consultations, were published as final on 8 August 2016.

On 15 December 2015, revision 1 of Module XV on safety communication, with revision 1 of the Template for Direct Healthcare Professional Letters (DHPCs) and a new Template for DHPC-Communication Plans in GVP Annex II, and the second Product- or Population-Specific Considerations, namely P.II on biological medicinal products, were released for public consultation until 29 February 2016. The Considerations P.II were published as final, having been amended in the light of the public consultation, on 15 August 2016. The final revision 1 of Module XV on safety communication and the Templates were published on 12 October 2017, taking into account comments received during the public consultation.

On 29 February 2016, revision 2 of Module V on risk management system was released for public consultation until 31 May 2016 and published as final, taking into account the consultation comments, on 30 March 2017. At the same time, Module XVI was published in its revision 2 to delete the description of routine risk minimisation tools, as these had been detailed in GVP Module V, and to give further clarifications on some aspects on risk minimisation.

On 8 August 2016, draft revision 2 of Module VI on management and reporting of adverse reactions and draft revision 1 of Module IX on signal management with its Addendum were released for public consultation until 14 October 2016. Revision 2 of Module VI was finalised with amendments in the light of the public consultation and published on 2 August 2017. Its Addendum on the duplicate management of suspected adverse reaction reports was likewise published on 2 August 2017 as new guidance in GVP, based on a previous guideline published before GVP came into existence. Revision 1 of Module IX on signal management and its Addendum on methods were published as final on 12 October 2017, taking into account comments received during the public consultation. All these documents, i.e. revised Modules VI and IX and their Addenda, came into effect on 22 November 2017, together with the new Eudra Vigilance functionalities and application of the ICH-E2B(R3) guideline.

On 30 March 2017, Module II was published as revision 2 with updates in relation to outdated

transitionary guidance, the new Article 57 database and a few aspects to be clarified regarding the pharmacovigilance systems master file (PMSF).

On 12 October 2017, revision 3 of Module VIII on PASS was published in order to align this Module with the recently published revision 2 of Module VI. Revision 4 of the Annex I on definitions was published, mainly with terms introduced by Regulation (EU) No 536/2014 Art 2(2)(1) on clinical trials and other terms relevant to recently developed or revised GVP documents. An updated Annex V on abbreviations was published too.

A public consultation was launched for new Product- or Population-Specific Considerations, namely on the paediatric population, on 2 August 2017 until 13 October 2017. This Considerations Chapter P IV was based on a guideline published before GVP came into existence and was the first GVP Chapter focussing on a specific population group. Taking into account the comments received during the public consultation, it was finalised and published on 7 November 2018.

Objectives of pharmacovigilance

Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

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

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

Pharmacovigilance in the EU: roles of different actors

In the EU, a regulatory network, consisting of the competent authorities in Member States, the European Commission and the European Medicines Agency (in GVP referred to as "the Agency") is responsible for granting marketing authorisations and supervising medicinal products, including the

conduct of pharmacovigilance. The Agency has a core role in coordinating these activities for the network.

In addition to the network's responsibilities, EU legislation imposes responsibility for pharmacovigilance, together with specific obligations (i.e. in terms of tasks and responsibilities), on marketing authorisation holders.

In the past, the role of healthcare professionals was mainly seen as contributing to pharmacovigilance through spontaneous reporting of suspected adverse reaction cases and as receiving, together with the patients, advice on minimising risks through updated product information or other information materials. However over time, participation of patients and healthcare professionals in EU regulatory processes, including those for pharmacovigilance, has steadily increased. A large number of Member States have established, over the last years, schemes for reporting of suspected adverse reactions by patients themselves. An EU legal framework for patient reporting in all Member States has now been introduced through the new pharmacovigilance legislation. The new legislation further increases public participation by including patient and healthcare professional representatives in the new Pharmacovigilance and Risk Assessment Committee (PRAC) and through public hearings on pharmacovigilance and benefit-risk matters at the Agency, involving all stakeholders.

Legal basis, scope and process for GVP

The legal framework for pharmacovigilance of medicinal products for human use in the EU is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended in 2010 by Regulation (EU) No 1235/2010 and Directives 2010/84/EU and 2012/26/EU respectively, as well as by the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. It should be noted that Chapter 3 of the Regulation (EC) No 726/2004 as amended, Title IX of the Directive 2001/83/EC as amended and the Implementing Regulation contain the majority of pharmacovigilance provisions in the legislation, however, other measures directly relevant to the conduct of pharmacovigilance are found in other Chapters and Titles of this Regulation and Directive.

The aforementioned amending legislation of 2010/12, together with the related Implementing Regulation, is commonly referred to as the new pharmacovigilance legislation in the EU. It was the outcome of a major review of the current pharmacovigilance system in the EU conducted by the European Commission, followed by a formal law-making process in the Council and European

Parliament. The legislation has the primary aim to strengthen and rationalise pharmacovigilance and increase patient safety.

The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product unless specific provision or exemptions apply as indicated in the GVP chapters.

GVP is drawn up to facilitate the performance of pharmacovigilance activities within the EU and applies to marketing authorisation holders in the EU, the Agency and competent authorities in Member States. Where in GVP reference is made to Member States of the EU, this should be read to include Iceland, Liechtenstein and Norway. These countries have, through the Agreement of the European Economic Area (EEA), adopted the complete Union acquis (i.e. the legislation at EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. The new pharmacovigilance Regulation (EU) No 1235/2010 and Directive 2010/84/EU have likewise been implemented in these countries[1].

GVP is drawn up based on Article 108a(a) of Directive 2001/83/EC as amended, by the Agency in cooperation with competent authorities in Member States and interested parties.

GVP is being developed within a governance structure set up by the Agency and national competent authorities specifically for the implementation of the new pharmacovigilance legislation. This structure allows for the close collaboration of Member States, the Agency and the European Commission services, with regular stakeholder meetings an integral part of the implementation process.

Each draft chapter of GVP is prepared by a project team (Modules) or author team (Considerations) consisting of experts from Member States and the Agency, taking into account comments collected during the stakeholder meetings. The draft chapters are agreed by the Heads of Medicines Agencies'

EU Network Pharmacovigilance Oversight Group (EU-POG) (until 2016 by the European Risk Management Strategy Facilitation Group (ERMS FG)) and are released for public consultation on behalf of the EU regulatory network. After public consultation, the chapters are finalised within the governance structure, addressing the comments from stakeholders, and then published by the Agency.

Maintenance and further development of GVP

Proposals for corrections, revision/addition of guidance or new GVP chapters can be made by any member of the EU regulatory network as well as any other stakeholder. There might not be an

immediate, individual response, but all proposals will be reviewed regularly and prioritised within the governance structure set up by the Agency and national competent authorities for the implementation of the new pharmacovigilance legislation.

Structure of GVP

Pharmacovigilance activities are organised by distinct but connected processes, and each GVP Module presents one major pharmacovigilance process. In addition, GVP provides guidance on the conduct of pharmacovigilance for specific product types or specific populations in which medicines are used. These GVP Considerations apply in conjunction with the process-related guidance in the Modules.

While the development of GVP is ongoing, some guidelines developed under the previous legislation remain valid in principle (unless any aspect is not compatible with the new legislation) until they are revised at a later point in time for inclusion in GVP. They are published on the Agency's GVP webpage under GVP Annex III.

Within each chapter, Section A provides the legal, technical and scientific context of the respective process. Section B gives guidance which, while based on EU legislation, reflects scientific and regulatory approaches, formats and standards agreed internationally in various for a; or, where such formal agreements or expert consensus do not exist, Section B describes approaches which are considered in line with general current thinking in the field. Section C focusses on the specifics of applying the approaches, formats and standards in the EU and other aspects of operating the respective process in the EU.

In particular in Sections B, the term "competent authority" is to be understood in its generic meaning of an authority regulating medicinal products and/or an authority appointed at national level for being in charge of all or individual pharmacovigilance processes. For the purpose of applying GVP in the EU, the term "competent authority" covers the competent authorities in Member States and the Agency.

<u>Good Pharmacovigilance practices (GPP)</u>

Introduction

This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorisation holders, competent authorities of Member States and the Agency. How the systems of these organisations interact while undertaking specific pharmacovigilance processes is described in each respective Module of

GVP.

The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.

For performing their pharmacovigilance activities, marketing authorisation holders, competent authorities of Member States and the Agency shall establish and use quality systems that are adequate and effective for this performance. The legal requirement for quality systems was introduced by Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced as DIR) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG) to strengthen pharmacovigilance in the EU. The minimum requirements of these quality systems are set out in the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (the Implementing Regulation is referenced as IR).

While there has to be compliance with these legal requirements, the implementation of a quality system should be adapted to the respective organisation.

By following the overall quality objectives in I.B.4. and the guiding principle in I.B.5. to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each medicinal product covered by a quality system.

The guidance on quality systems in this Module is consistent with the general principles of the ISO 9000 Standards on good quality management practices, specifically the ISO 9001-2008 Standards on quality management systems, issued by the International Organization for Standardization (ISO). The general application of quality management to pharmacovigilance systems is described under I.B. and requirements specific to the operation of the EU network in I.C..

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

I.A. Structures and processes

I.A.1. *Pharmacovigilance system*

A pharmacovigilance system is defined as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR Art 1(28d)].

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

I.A.2. *Quality, quality objectives, quality requirements and quality system*

For the purpose of GVP, which provides guidance on structures and processes of a pharmacovigilance system, the quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under I.B.4..

Specific quality objectives and quality requirements for the specific structures and processes of the pharmacovigilance systems are provided in each Module of GVP as appropriate.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management [IR Art 8(2)].

I.A.3. *Quality cycle*

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

- quality planning: establishing structures and planning integrated and consistent processes;
- quality adherence: carrying out tasks and responsibilities in accordance with quality requirements
- quality control and assurance: monitoring and evaluating how effectively the structures

and processes have been established and how effectively the processes are being carried out; and

- quality improvements: correcting and improving the structures and processes where necessary [IR Art 8(3)].

I.A.4. *Overall quality objectives for pharmacovigilance*

The overall quality objectives of a pharmacovigilance system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

I.A.5. *Principles for good pharmacovigilance practices*

With the aim of fulfilling the overall quality objectives in I.B.4., the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.
- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All persons within the organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in I.B.3..
- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of

pharmacovigilance.

- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

I.A.6. *Responsibilities for the quality system within an organisation*

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities [IR Art 10(1), Art 14(1)]. Their responsibility should include adherence to the principles defined in I.B.5..

For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:

- ensuring that the organisation documents the quality system as described in I.B.11.;
- ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- ensuring that adequate resources are available and that training is provided (see I.B.7.);
- ensuring that suitable and sufficient premises, facilities and equipment are available (see I.B.8.);
- ensuring adequate compliance management (see I.B.9.);
- ensuring adequate record management (see I.B.10.);
- reviewing the pharmacovigilance system including its quality system at regular intervals in risk- based manner to verify its effectiveness (see I.B.12.) and introducing corrective and preventive measures where necessary;
- ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organisation;
- identifying and investigating concerns arising within an organisation regarding suspected non- adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see I.B.12.).

In relation to the management responsibilities described above, upper management within an organisation should provide leadership through:

- motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation; and
- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

For competent authorities, all persons involved in the procedures and processes of the quality system established for the performance of pharmacovigilance activities shall be responsible for the good functioning of that quality system and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system [IR Art 8(5)].

I.A.7. *Training of personnel for pharmacovigilance*

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see I.B.6.).

All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training [IR Art 10(3), Art 14(2)]. For marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel [IR Art 10(3)].

The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel [IR Art 10(3), Art 14(2)]. Training plans should be based on training needs assessment and should be subject to monitoring.

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

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

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

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.), shall be provided by the organisation to their personnel [IR Art 10(4), Art 14(3)].

I.A.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance 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 (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see I.B.4.) and also be available for business continuity (see I.B.11.3.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies (see Module VI) in their valid versions and to keep the IT systems up-to-date accordingly.

I.A.9. Specific quality system procedures and processes

I.A.9.1. Compliance management by marketing authorisation holders

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

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder [IR Art 11(1)(a)] (see Modules IX and XII);
- the scientific evaluation of all information on the risks of medicinal 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 authorisation or associated

with occupational exposure [IR Art 11(1)(b)] (see Modules VI, VII, VIII, IX);

- the submission of accurate and verifiable data on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits [IR Art 11(1)(c)] (see Modules VI and IX);
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals [IR Art 11(1)(d)] (see Modules V, VI, VII, VIII and IX);
- effective communication by the marketing authorisation holder with competent authorities, including communication on new or changed risks (see Module XII and XV), the pharmacovigilance system master file (see Module II), risk management systems (see Module V), risk minimisations measures (see Modules V and XVI), periodic safety update reports (see Module VII), corrective and preventive actions (see Modules II, III and IV) and post-authorisation safety studies (see Module VIII) [IR Art 11(1)(e];
- the update of product information by the marketing authorisation holder in the light of scientific knowledge [IR Art 11(1)(f)] (see Module XII);
- appropriate communication of relevant safety information to healthcare professionals and patients (see Module XII and XV) [IR Art 11(1)(g)].

I.A.9.2. Compliance management by competent authorities

For the purpose of compliance management, competent authorities shall establish specific quality system procedures and processes in order to achieve all of the following objectives:

- ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted [IR Art 15(1)(a)];
- ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines [IR Art 15(1)(b)];
- ensuring independence in the performance of pharmacovigilance activities [IR Art 15(1)(c)];

- ensuring effective communication with patients, healthcare professionals, marketing authorisation holders and the general public [IR Art 15(1)(d)];
- conducting inspections, including pre-authorisation inspections [IR Art 15(1)(f)].

Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on medicinal products should be taken in the sole interest of patients' and public health.

I.A.10. *Record management*

The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information [IR Art 12(1), Art 16(1)].

A record management system shall be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process [IR Art 12(1), Art 16(1)].

The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;
- effective internal and external communication; and
- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports [IR Art 12(1)].

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process (IR Recital 17). As part of a record management system,

specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

The record management system should be described in a record management policy.

Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records [IR Art 8(4)].

A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the organisation should define in advance:

- quality objectives specific to their organisations in accordance with the overall quality objectives provided under I.B.4. and the structure- and process-specific quality objectives in accordance with each Module of GVP; and
- methods for monitoring the effectiveness of the pharmacovigilance system (see I.B.12.).

The quality system shall be documented by:

- documents on organisational structures and assignments of tasks to personnel (see I.B.11.1. and I.B.11.2.);
- training plans and records (see I.B.7.) [IR Art 10(3), Art 14(2)];
- instructions for the compliance management processes (see I.B.9.) [IR Art 11(1), Art 15(1)];
- appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.) [IR Art 10(4), Art 14(3)];

- performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)];
- reports of quality audits and follow-up audits, including their dates and results [IR Art 13(2), Art 17(2)].

Training plans and records shall be kept and made available for audit and inspection [IR Art 10(3), Art 14(2)].

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

- the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- a record management policy;
- records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
- records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

I.A.10.1. Additional quality system documentation by marketing authorisation holders

In addition to the quality system documentation in accordance with I.B.11., marketing authorisation holders shall document:

- their human resource management in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(b)];
- job descriptions defining the duties of the managerial and supervisory staff [IR Art 10(2)];
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff [IR Art 10(2)];
- instructions on critical processes (see I.B.11.3.) in the pharmacovigilance system master

file (PSMF) (see Module II); and

- their record management system in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(c)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

For the requirements of documenting the quality system in the pharmacovigilance system master file (PSMF) or its annexes, see Module II.

I.A.10.2. Additional quality system documentation by competent authorities

In addition to the quality system documentation in accordance with I.B.11., the organisational structures and the distribution of tasks and responsibilities shall be clear and, to the extent necessary, accessible [IR Art 14(1)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

Contact points shall be established [IR Art 14(1)], in particular to facilitate interaction between competent authorities, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.

I.A.10.3. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk- benefit balance of products for the aim of safe and effective use of medicinal products;
- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and competent authorities.

I.B.12. *Monitoring of the performance and effectiveness of the* pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its

quality system should include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;
- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.

The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)] in relation to the quality requirements. The quality requirements for each pharmacovigilance process are provided in each Module of GVP as appropriate.

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see I.B.11.) at regular intervals, with the frequency and the extent of the reviews to be determined in a risk-based manner. Pre-defined programmes for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness [IR Art 13(1), Art 17(1)]. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in Module IV. In relation to the pharmacovigilance system of a marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited [IR Art 13(2)]. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder‘s pharmacovigilance system. For competent authorities, the audit report shall be sent to the management responsible for the matters audited [IR Art 17(2)].

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary [IR Art 13(2),

Art 17(2)]. Additionally, the competent authorities should have in place arrangements for monitoring the compliance of marketing authorisations holders with legally required pharmacovigilance tasks and responsibilities. They shall further ensure compliance with the legal requirements by means of conducting inspections of marketing authorisation holders [DIR Art 111(1)] (see Module III). Guidance on compliance monitoring for each pharmacovigilance process is provided in each Module of GVP as appropriate.

Requirements and methods for evaluating the effectiveness of actions taken upon medicinal products for the purpose of minimising risks and supporting the safe and effective use of medicines in patients are described in Module XVI.

I.B.13. *Preparedness planning for pharmacovigilance in public health* emergencies

Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

Expedited Reporting Requirements:

Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via
AdEERS within the timeframes detailed in the table below.

Grade 1 and 2 Timeframes	Grade 3-5 Timeframes.
10 Calendar Days	24-Hour 5 Calendar Days

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for **ALL** Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution.

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Expedited Reporting Requirements (cont.)

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Appendix 1: Expedited Reporting Requirements (cont.)

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Question Bank

1. Describe the Role of Pharmacovigilance in Drug Regulation?
2. Write down the Regulatory aspects in Pharmacovigilance?
3. Discuss Good Pharmacovigilance practices?
4. Give an essay on Expedited reporting requirements?

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(INTERNATIONAL RESEARCH CENTRE)

UNIT – IV - Pharmacovigilance in India other countries – SMB5401

Subject Name: Pharmacovigilance and Safety monitoring **Subject Code: SMB5401**

Unit - IV

Pharmacovigilance centers in India

Pharmacovigilance is a pharmacological science related to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines. It has been observed that a medication that is proven efficacious in large patient population often fails to work in some other patients of different ancestry. Ancestral background of the patients are controlled by genetic factors that influence drug response-drug targets, drug-metabolizing enzymes, drug transporters, and genes indirectly affecting drug action can modulate drug toxicity and contribute to its individual variability. Thus, adverse drug reactions are highly variable in individuals and are major limiting factor in drug therapy and development. Therefore, even though the drug had already been approved in some other country, clinical trial with robust pharmacovigilance monitoring is needed in the population of different race & ethnicity.

In India, a formal ADR monitoring system was started in 1986 with 12 regional centers. In 1997, India became the member of WHO Programme for International Drug Monitoring managed by the Uppsala Monitoring Centre (UMC), Sweden. At inception, 6 regional centers were set up in Mumbai, New Delhi, Kolkata, Lucknow, Pondicherry, and Chandigarh for ADR monitoring in the country. Of these 6 centers, only the centers in Mumbai and New Delhi were active and thus spontaneous reporting of ADRs were poor. Therefore, in November 2004, Govt. of India has launched National Pharmacovigilance Programme (NPvP) with an annual grant of US$0.1 million approved for 5 years from World Bank. However, the World Bank funding for this programme was ended in mid-2009 and this programme was temporarily suspended. Recognizing the need for improved ADR monitoring in the country, in July, 2010, under the aegis of Health Ministry, a nation-wide revised ADR monitoring programme was launched and named as Pharmacovigilance Programme of India (PvPI). Initially, under this National programme, All India Institute of Medical Sciences, New Delhi was the National Coordination Centre (NCC) and in April, 2011, it was shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad. Dr. G. N. Singh, Scientific Director of IPC was designated as a National Coordinator of PvPI for ADR monitoring in the country. Under PvPI, ADRs are being identified and spontaneously reported by the healthcare professional of Adverse Drug Reaction Monitoring Centres (AMC). These AMCs responsible for

collecting adverse event as per Standard Operating Procedure (SOP), performing follow up if require for the completeness of ADR reports and uploading these reports in netbased software used for ADR reporting called as Vigiflow. These drug safety information/Individual Case Safety Reports (ICSRs) are collected in predesigned suspected ADR reporting form, broadly consist of 4 sections i.e., patient's information, suspected adverse reaction, suspected medication(s), and reporter's information. These ICSRs are then reported to NCC for Quality & Signal Review via Vigiflow after causality assessments of ADRs performed using the WHO-UMC causality assessment system (Figure 1). The purpose of this programme is to collect, collate and analyze this reported data to arrive at an inference to recommend regulatory interventions for safeguarding the health of Indian population by ensuring that benefit outweighs the risks associated with the use of medicines. Under PvPI, AMC plays a vital role in collection and follow-up of ADR reports from healthcare professionals. Initially there were 22 AMCs in the country.

At present there are 150 AMCs under this programme and categorized into four zones i.e., North, South, East and West (Pharmacovigilance Programme of India (PvPI) newsletter, 2013) 1. In coming year, there will be 350 AMCs across the country to make this programme one of the largest Pharmacovigilance Programme in the world. Under previous National Pharmacovigilance Programme, 11633 ICSRs were reported from January 2006 to December 2008 whereas under PvPI, till June 2014, 78672 ICSRs are reported. Thus, it can be observed that the rate of reporting has been increased under PvPI. The safety database of PvPI is growing with the increase in number of AMCs in each year. This database allows healthcare providers and consumers to browse and view data on suspected adverse drug reactions of various medicinal products. All data contained herein is sourced from VigiBase R , the WHO global database for ADRs, maintained by the UMC, to make drug safety information available for Indian population. Beside suspected ADR reporting form, PvPI have developed medicine side effect reporting form for consumers/patients in their regional language. PvPI have also extended its reach to other National Health Programmes within country. National coordinating center has collaborated with Revised National Tuberculosis Control Programme and National Aids Control Organization to monitor the safety of drugs use in their programme.

Under PvPI, several drugs are under scanner and quarterly drug safety alerts on suspected unexpected serious adverse reactions (SUSARs) are issued to healthcare professionals via newsletters (Table 1). Based upon PvPI database, this year Drugs Controller of India has instructed manufacturers to include Steven Johnson Syndrome (SJS) in package insert of

product containing carbamazepine and advised to the physicians to screen the patients for HLA-B*1502 allele before initiating treatment with carbamazepine. However, India doesn't have a strong database on ADRs and has to depend on data from Western countries to take decisions relating to banning and suspension of drugs.

The present database of PvPI available on ADRs is not sufficient to represent the population which consumes the drug or to which the drug has been prescribed for. Epidemiological data on drug utility and outcomes of treatments is inadequate. Therefore, for sufficient database on ADRs, awareness among the healthcare providers of government and corporate hospitals including rural areas are needed to be created. The other healthcare institutes like dental, pharmacy, nursing, paramedical etc. associated with patients care by providing safe and effective medication should be encouraged for ADR reporting. Beside these, pharmaceutical companies need to be involved in PvPI for better pharmacovigilance system. Furthermore, incorporating a chapter on pharmacovigilance in education curriculum of medicine, pharmacy, nursing etc. could generate the culture of ADR reporting among young scholars. It was observed that the percentage of ADR reporting by physicians was higher as compare to pharmacists and other healthcare providers.

In India, system of distribution does not leave much scope for pharmacists, nurses, and other healthcare providers to be a significant source of ADR reporting. Even though nurses are in closer contact with the patients for a longer duration, in the event of ADRs observed by them, they have to inform to the treating physician. Similarly, pharmacist's can also promote the development, maintenance, and ongoing evaluation of a programme to reduce the risks of ADRs by detecting, reporting, and assessing any suspected ADRs. Therefore, co-ordination among clinician, pharmacist, and nurse appears vital in contributing each of their respective expertise and experience to promote the rational use of medicines. It was also observed that the lack of knowledge of where, what and how ADRs should be reported is also affects reporting. The reason for poor reporting may also include financial incentives, ignorance (only serious ADRs are to be reported), apprehension of reporting serious ADRs, and lack of time or over load. Thus, healthcare professionals should be under an obligation to report ADR if detected while clinical practice. However, several steps are taken to tackle the problems of under reporting by addressing various issues in various forum and conferences, circulating questionnaire form, writing to professional bodies, scientific journals, etc. In an effort to extent awareness among healthcare providers, continues medical education are being organized in various medical colleges across the country.

In addition, Technical Associates are recruited at AMC to facilitate ADR reporting from healthcare providers. In year 2013, India's contribution to WHO–UMC's global drug safety database (Vigibase) was 2%. India was 7th in position among top 10 counties contributing to global drug safety database. Among Asian countries, India is the only country having more than 1 lakhs ICSRs in Vigibase. According to WHOUMC Documentation Grading-Completeness Score, the average completeness score of India in 3rd quarter of 2014 was 0.94 out of 1 [(WHO-Uppsala Monitoring Centre (UMC), 2014)]. Thus, from this completeness score it can be predicted that AMCs of PvPI are collecting all the necessary information required for ADR reporting via Vigiflow. In conclusion, awareness about the ADR reporting among the healthcare providers can improve the rate of reporting across the country. Moreover, by developing own national database and sharing information with other regulatory agencies will provide the much needed information from worldwide data to take the correct decision on medicines and products.

Central Drugs Standard Control Organization (CDSCO)

The Central Drugs Standard Control Organization (CDSCO) is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the European Medicines Agency of the European Union, the PMDA of Japan, the Food and Drug Administration of the United States and the Medicines and Healthcare products Regulatory Agency of the United Kingdom. The government has announced its plan to bring all medical devices, including implants and contraceptives, under the view of the Central Drugs and Standard Control Organisation (CDSCO) But Some instruments, Equipment's with IVD will not cover in Medical Device rule Such as hemoglobinometer based micro cuvette technology which is reagent free because Micro cuvette is under the category of plastic disposable which is only used for sample collection and this category is not regulated under the provision of Class II of IVD Medical device rules. Strips work on single wavelength Microcuvette technology works on dual wavelength. There is 1 wavelength for HB measurement and another for turbidity compensation. This ensures accuracy even in turbid samples. Cuvette technology, shelf life for both open and unopened vials is 24 months. Strips usually have a shelf life of 12 months for unopened vials and for open vials it's around 3 months. Hence chances of expiry with cuvette technology is much less.

Within the CDSCO, the Drug Controller General of India (DCGI) regulates pharmaceutical and medical devices, under the gamut of Ministry of Health and Family Welfare. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC). It is divided into zonal offices which do pre-licensing and post-licensing inspections, post-market surveillance, and recalls when needed. Manufacturers who deal with the authority are required to name an Authorized Indian Representative (AIR) to represent them in all dealings with the CDSCO in India.

Though the CDSCO has a good track record with the World Health Organization, it has also been accused of past collusion with independent medical experts and pharmaceutical companies.

Indian PV guidelines-National Pharmacovigilance Program (NPP)

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Abbreviations

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

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

A. INTRODUCTION

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

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

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

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

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

A.1 Objective

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

A. 2 Scope

This document includes following category of pharmaceutical products:

- New Drugs, subsequently approved drugs.

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

This guidance document excludes veterinary products and medical devices.

B. ROLES AND RESPONSIBILITIES OF AUTHORITIES

B.1 Central Drugs Standard Control Organization

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

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

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

B.1.1 State Drug Control Authority:

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

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

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

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

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

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

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

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

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

B.2.1 PvPI - Programme Communication

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

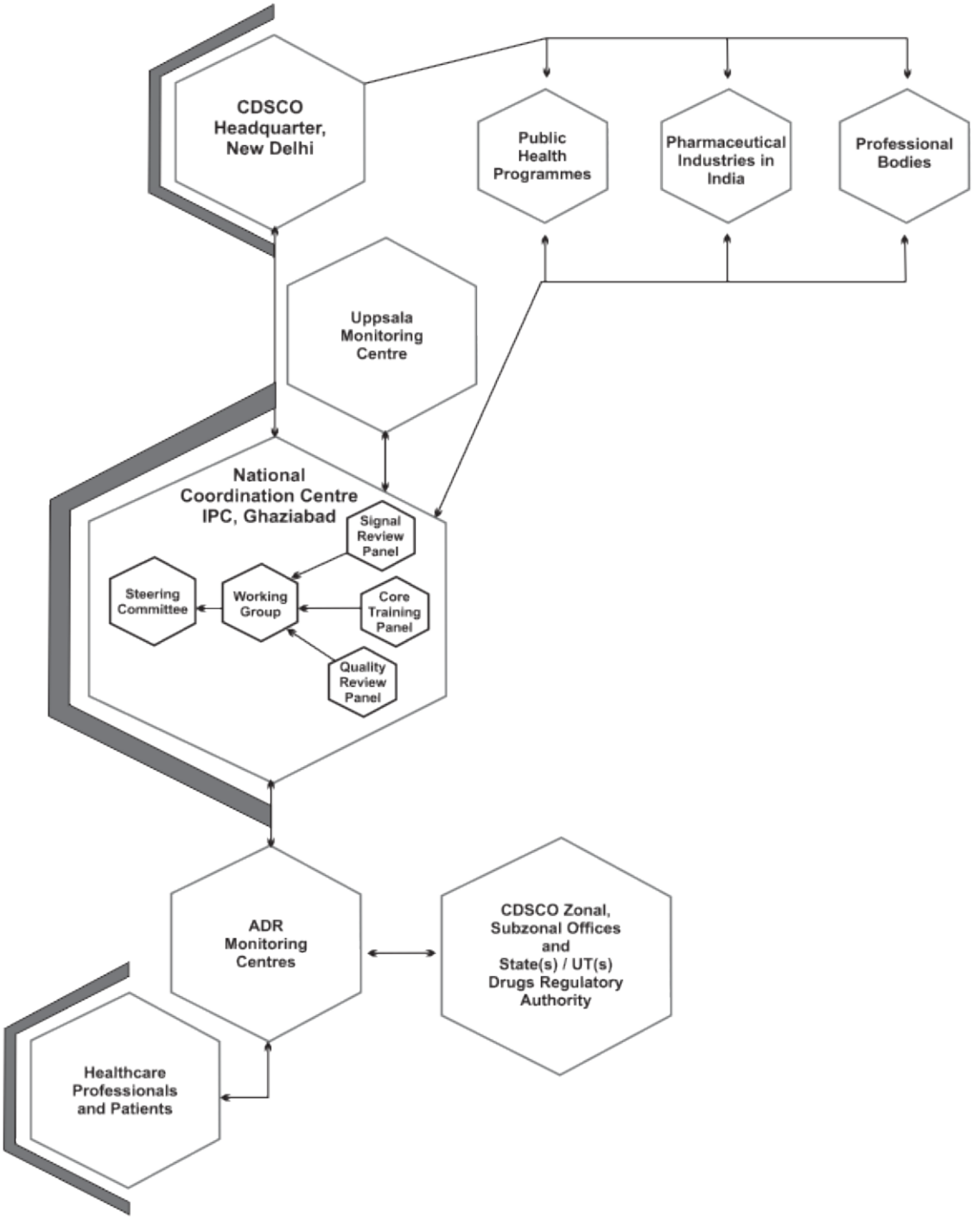

Figure 1: PvPI-Programme Communication

C. MODULES

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

MODULE 1

Pharmacovigilance System Master File

Contents:

1.1 Introduction

1.2 Scope

1.3 Objectives

1.4 Content of the PvMF

1.4.1 Pharmacovigilance Officer In-charge

1.4.2 Pharmacovigilance organization structure

1.4.3 Sources of safety data

1.4.4 Pharmacovigilance processes

1.4.5 Pharmacovigilance system performance

1.5 Annexures to the PvMF

1.1 Introduction

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

1.2 Scope

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

1.3 Objective

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

1.4 Contents of the PvMF

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

1.4.1 Pharmacovigilance Officer In-charge

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

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

1.4.2 Pharmacovigilance organization structure

1.4.2.1 MAH

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

1.4.2.2 Contract Research Organization

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

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

1.4.3 Sources of safety data

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

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

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

1.4.4 Pharmacovigilance Processes

1.4.4.1 Description

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

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

1.4.4.2 SOP should include the following:

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

1.4.4.3 Computerized systems and database

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

1.4.4.4 QMS in Pharmacovigilance

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

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

1.4.5 Pharmacovigilance system performance

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

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

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

1.5 Annexures to the PvMF

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

MODULE 2

Collection, Processing & Reporting of Individual Case Safety Reports

Contents:

2.1 Introduction

2.2 Structure & Processes

2.3 Literature monitoring

2.4 Follow-up ICSR

2.5 Processing of ICSR

2.6 Reporting of ICSR

2.7 Coding

2.8 Reporting time frames

2.9 Causality assessment

2.10 Special Population

2.1 Introduction

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

2.2 Structure & Processes

2.2.1 Collection of ICSR

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

2.2.1.1 Medical inquiries

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

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

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

2.2.1.3 MAH's employees

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

2.2.1.4 Contractual partners

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

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

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

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

2.2.1.6 Solicited reports

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

2.2.1.7 Miscellaneous sources for reporting

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

2.3 Literature monitoring

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

2.4 Follow-up ICSR

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

2.5 Processing of ICSR

2.5.1 ICSR receipt

2.5.1.1 Date of receipt

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

2.5.1.2 Validation of reports

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

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

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

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

2.6 Reporting of ICSR

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

2.6.1 Essential data elements of ICSR

Each ICSR should contain the following mandatory fields:

2.6.1.1 Patient information

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

2.6.1.2 Suspected reaction

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

2.6.1.3 Suspected medication(s)

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

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

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

- Drug withdrawn

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

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

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

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

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

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

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

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

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

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

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

2.6.1.4 Reporter

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

2.7 Coding

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

2.8 Reporting time frames

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

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

2.9 Causality assessment

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

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

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

2.10 Special population

2.10.1 Use of a pharmaceutical product during pregnancy or breastfeeding

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

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

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

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

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

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

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

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

MODULE 3

Preparation & Submission of Periodic Safety Update Report

Content:

3.1 Introduction

3.2 Objective

3.3 General principles

3.4 Structure & content

3.1 Introduction

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

3.2 Objective

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

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

3.3 General principles

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

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

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

(b) Relate these data to patient exposure;

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

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

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

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

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

3.4 Structure & content

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

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

9.3 Overview of Signals: New, Ongoing, or Closed

10. Overall Safety Evaluation

10.1 Signal and Risk Evaluation

10.2 Benefit Evaluation

10.3 Benefit-Risk Analysis Evaluation

11. Conclusions

12. Appendix to the PSUR

1. Title Page

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

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

2. Introduction

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

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

3. Current worldwide marketing authorization status

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

4. Update of actions taken for safety reasons

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

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

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

Actions related to drugs after approval

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

5. Changes to Reference Safety Information

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

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

6. Estimated patient exposure

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

6.1 Cumulative subject exposure in clinical trials

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

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

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

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

6.2 Cumulative and interval patient exposure from marketing experience in India

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

The data should be presented according to the following categories:

6.2.1 Post-approval (non-clinical trial) exposure

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

6.2.2 Post-approval use in special population

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

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

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

6.2.3 Other post-approval use

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

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

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

7. Presentation of individual case histories

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

7.1 Line listing of individual cases received from India

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

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

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

7.3 Cumulative summary tabulations of serious adverse events from clinical trials

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

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

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

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

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

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

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

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

8. Studies

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

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

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

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

8.1.1 Completed clinical trials

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

8.1.2 Ongoing clinical trials

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

8.1.3 Long-term follow-up

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

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

8.1.4 Other therapeutic uses of pharmaceutical product

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

8.1.5 New safety data related to fixed combination therapies

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

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

8.2 Findings from non-interventional studies

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

8.3 Information from other clinical trial sources

8.3.1 Other clinical trials

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

8.3.2 Medication errors

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

8.4 Findings from non-clinical studies

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

8.5 Findings from literature

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

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

This should include:

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

9. Other Information

9.1 Lack of efficacy in controlled clinical trials

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

9.2 Late-breaking information

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

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

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

9.3 Overview of signals: new, ongoing, or closed

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

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

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

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

10. Overall safety evaluation

10.1 Signal and risk evaluation

The purpose of this section is to provide:

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

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

10.1.1 Summary of safety concerns

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

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

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

10.1.2 Signal evaluation

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

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

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

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

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

10.1.3 Evaluation of risks and new information

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

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

New information can be organized as follows:

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

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

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

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

10.1.4 Characterization of risks

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

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

10.1.5 Effectiveness of risk minimization (if applicable)

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

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

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

10.2 Benefit evaluation

10.2.1 Important baseline efficacy/effectiveness information

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

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

10.2.2 Newly identified information on efficacy/effectiveness

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

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

10.2.3 Characterization of benefits

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

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

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

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

10.3 Benefit-Risk analysis evaluation

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

10.3.1 Benefit-Risk context - medical need and important alternatives

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

10.3.2 Benefit-Risk analysis evaluation

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

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

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

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

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

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

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

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

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

11. Conclusions

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

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

12. Appendix to the PSUR

A PSUR should contain the following appendix as appropriate:

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

MODULE 4

Quality Management System at Marketing Authorization Holder Organization

Contents:

4.1 Introduction

4.2 Scope

4.3 Structures and Processes

4.4 Specific quality system procedures and processes

4.1 Introduction

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

4.2 Scope

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

4.3 Structures and Processes

4.3.1 Pharmacovigilance system

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

4.3.2 Quality cycle of Pv system

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

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

4.3.3 Quality objectives for Pv

The overall quality objectives of a Pv system are:

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

4.3.4 Responsibilities for the quality system within an organization

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

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

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

4.3.5 Training of MAH personnel for Pv

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

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

4.3.6 Facilities and equipment for Pv

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

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

4.4 Specific quality system procedures and processes

4.4.1 Compliance management by MAH

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

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

4.4.2 Record management

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

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

4.4.3 Documentation of the quality system

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

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

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

the quality objectives;

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

4.4.4 Critical Pv processes and business continuity

The following Pv processes should be considered as critical include:

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

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

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

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

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

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

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

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

Refer Module 1 for detailed information .

MODULE 5

Audit & Inspection of Pharmacovigilance System at Marketing Authorization Holder Organization

Contents:

5.1 Introduction

5.2 Objectives

5.3 Inspection Types

5.4 Inspection Procedure

5.5 Regulatory Actions

5.6 Training Inspectors

5.1 Introduction

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

5.2 Objectives

The objectives of Pv audits and inspections are as below:

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

  Inspections broadly cover the following:

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

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

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

5.3 Inspection Types

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

5.3.1 Routine inspection

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

5.3.2 Targeted inspections

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

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

5.4 Inspection Procedure

5.4.1 Inspection Planning

Pv inspection should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency and scope of inspections to be determined accordingly. Pv inspection may be done by the officials responsible for inspection.

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

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

5.4.2 Organization to be inspected

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

5.4.3 Inspection procedures

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

5.4.4 Inspection findings

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

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

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

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

5.4.5 Inspection follow-up

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

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

5.4.6 Responding to inspection findings

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

5.5 Regulatory actions

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

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

5.6 Training of Inspectors

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

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

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

MODULE 6

Submission of Risk Management Plan

Contents:

6.1 Introduction

6.2 Objectives

6.3 Content of RMP

6.1 Introduction

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

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

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

6.2 Objectives

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

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

To fulfil above objectives a RMP should also:

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

6.3 Content of RMP

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

RMP should contain following sections:

6.3.1 Pharmaceutical product overview

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

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

6.3.2 Safety specifications

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

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

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

6.3.2.2 Non-clinical part of the safety specification:

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

6.3.2.3 Clinical trial exposure:

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

6.3.2.4 Populations not studied in clinical trials:

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

6.3.2.5 Post-marketing experience:

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

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

6.3.2.6 Identified and potential risks:

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

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

6.3.2.7 Summary of the safety concerns:

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

6.3.3 Pv activities

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

6.3.4 Risk minimization activities

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

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

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

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Worldwide Unique No. :

Report Type ☐ Initial ☐ Follow up

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent impairment/damage
☐ Hospitalization/Prolonged
☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
Iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

National Coordination Centre
Pharmacovigilance Programme of India
Ministry of Health & Family Welfare,
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
Tel.: 0120-2783400, 2783401, 2783392
Fax: 0120-2783311
www.ipc.nic.in

Pharmacovigilance Programme of India for Assuring Drug Safety

ADVICE ABOUT REPORTING

A. What to report

- Report serious adverse drug reactions. A reaction is serious when the patient outcome is:
  - Death
  - Life-threatening
  - Hospitalization (initial or prolonged)
  - Disability (significant, persistent or permanent)
  - Congenital anomaly
  - Required intervention to prevent permanent impairment or damage
- Report non-serious, known or unknown, frequent or rare adverse drug reactions due to Medicines, Vaccines and Herbal products.

B. Who can report

- All healthcare professionals (Clinicians, Dentists, Pharmacists and Nurses) can report adverse drug reactions

C. Where to report

- Duly filled Suspected Adverse Drug Reaction Reporting Form can be send to the nearest Adverse Drug Reaction Monitoring Centre (AMC) or directly to the National Coordination Centre (NCC).
- Call on Helpline (Toll Free) 1800 180 3024 to report ADRs.
- Or can directly mail this filled form to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com
- A list of nationwide AMCs is available at:
  http://www.ipc.gov.in, http://www.ipc.gov.in/PvPI/pv_home.html

D. What happens to the submitted information

- Information provided in this form is handled in strict confidence. The causality assessment is carried out at AMCs by using WHO-UMC scale. The analyzed forms are forwarded to the NCC through ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Centre in Sweden.
- The reports are periodically reviewed by the NCC-PvPI. The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.
- The information is submitted to the Steering committee of PvPI constituted by the Ministry of Health & Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

E. Mandatory field for suspected ADR reporting form

- Patient initials, age at onset of reaction, reaction term(s), date of onset of reaction, suspected medication(s) and reporter information.

For ADRs Reporting Call on PvPI Helpline (Toll Free)

1800 180 3024

(9:00 AM to 5:30 PM, Working Days)

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	Years		Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

ADVERSE DRUG REACTION REPORTING FORM

.

Sr. No

REPORT ON SUSPECTED SERIOUS ADVERSE DRUG REACTION

For Report to
Drugs Controller
Pak Secretariat, Block C,
Ministry of Health,

1. PARTICULARS OF PATIENT

Name of patient. _____

Age _____ Weight (kg) _____ Patient address _____

Sex ☐ Male Race _____

☐ Female

Pregnant ☐ Yes ☐ No ☐ Not applicable

Relevant Medical History _____

2. ADVERSE EVENT

Reason for reporting

☐ Requires or prolongs hospitalization ☐ Life threatening ☐ Death

☐ Permanently disabling or incapacitating ☐ Congenital anomaly ☐ Overdose

☐ Other (Please Specify) _____

3. SUSPECTED DRUG

Name of suspected Drug _____ Generic Name _____

Name of manufacturer _____

Date of occurrence _____ Duration of Event _____

Starting date of Medication _____

Route of administration _____

Discontinuation of Drug because of event ☐ No ☐ Yes Dated _____

4. REPORTING DOCTOR'S / PHARMACIST'S / NURSE'S SIGNATURE _____

Institution _____

Date _____

GUIDELINES TO FILL SERIOUS ADVERSE EVENT REPORT FORM

An adverse event is "Serious", if it

- Is life threatening
- Results in hospitalization
- Prolongation of hospitalization
- Causes malignancy
- Is an overdose resulting in clinically Relevant signs and / or symptoms
- Results in permanent disability
- Is associated with death
- Causes a birth defect
- Causes a relevant organ toxicity

An adverse drug event can be a manifestation of various etiologies such as

- Complication of an underlying disease
- Coincidental accident
- Concomitant medication
- Intercurrent disease
- Drug associated effect

List of abbreviations

AE	Adverse event
CT	Clinical trial
DDI	Drug-drug interaction
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
PV	Pharmacovigilance
SAE	Serious adverse event
TB	Tuberculosis
WHO	World Health Organization

1. Introduction

A **Serious Adverse Event (SAE)** is any untoward occurrence in a patient given a pharmaceutical product and that at any dose:

- Results in death,
- Is immediately life-threatening, meaning the patient was at risk of death at the time of the event. It does not apply to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of hospitalisation. This seriousness criterion does not apply to out-patient hospital visits.
- Results in persistent or significant disability/incapacity meaning a substantial disruption of patient's ability to carry out normal life activities.
- Is a congenital anomaly/birth defect in a child whose parent was exposed to a medicinal product prior to conception or during pregnancy.
- Is considered otherwise medically significant: other situation such as important medical events that may not immediately be life threatening or result in death or hospitalisation, but jeopardise the subject or require intervention to prevent one of the outcomes listed in the definition above, should also be considered serious (e.g. treatment in an emergency room for allergic bronchospasm). Medical judgment should always prevail in the assessment of medically significant events.

Any SAE as defined above occurring in the frame of a CT or a program sponsored by MSF is **reportable within 24 hours of awareness** to MSF Pharmacovigilance (PV) Unit using an SAE Report Form:

Email: PVunit.GVA@geneva.msf.org

Additional information on already transmitted SAEs, called follow-up information, should be reported similarly within 24 hours of awareness of the new information.

Unless described otherwise in the CT protocol or the program's PV guideline, **overdoses** are additionally reportable in an expedited manner (within 24 hours of awareness) to MSF PV Unit. An overdose is defined as the administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information or other in-use references (e.g. WHO guidelines). Clinical judgement should always be applied when evaluating whether an overdose was administered or not. The SAE Report Form should be used for overdose reporting even in the situations where the reported overdose did not lead to serious medical consequences.

Pregnancies are collected and reported using a dedicated form (Pregnancy Report Form) described in a separated guideline (Pregnancy Report Form completion guidelines).

In some CTs or programs, **other types of events** may require notification (e.g. AEs of special interest, medication errors). When no dedicated form is planned per CT protocol or program's PV guidelines, the SAE report form can be used for this purpose.

2 General instructions

The SAE Report Form is designed to allow for a proper case assessment and appropriate reporting in accordance with the applicable international standards (ICH E2B). The available fields must be completed as much as possible with the relevant information available at the time of reporting.

The minimal information to be reported includes:

1. Name or any identifier of a **reporter** (e.g. a function such as 'nurse' is acceptable),
2. Any identifier of the **patient** (e.g. patient number, initials, date of birth),
3. At least one **suspected drug** (study drug in a CT/ delivered drug in a program),
4. At least one **serious adverse event** (or overdose or any other safety information to be collected as per CT protocol/program's PV guideline).

The following general points aim at helping the completion of the SAE Report Form:

- Dates should be provided in the "Day/Month/Year" format: dd/Mmm/yyyy (e.g. 06/Apr/2015). If the exact date is not known, a partial date can be provided and the full date completed later upon follow-up (e.g. UNK/Apr/2015).
- In case you need to add more information than a field allows you to enter, please reprint the page, add manually the mention 'Supplemental page', and capture the additional information.
- Upon receipt of follow-up information on an SAE already notified (e.g. the patient has now fully recovered), the initial information does not need to be fully repeated on the SAE Report Form, only the new information with identifiers allowing to retrieve the initial information (site number, patient's identifiers, case number, diagnosis, etc.).
- In case corrections are needed, the correct vs. the incorrect information should be clearly identifiable and the correction should include the initials of the person who performed the modification and the date of such modification.
- All information about the patient must be anonymized in all documents before transmission to the MSF PV Unit.

As a general medical guideline, the following points should be considered:

- When several events are signs and symptoms grouped under a single **diagnosis**, the diagnosis should preferentially be reported. Relevant signs and symptoms can be described in the free-text field allowing for event's description (see section 13.6).
- In case **several reportable events** occurred at the same time in a same patient, it is upon the Investigator's/physician's judgment to report these on a same SAE Report Form or on separated SAE Report Forms.
  - Example 1, a patient is hospitalized with concomitant fever and nausea of unknown origin **->** it is advised to use of a single SAE Report Form mentioning fever and nausea.
  - Example 2, a patient experienced life-threatening anaphylactic shock during drug infusion, his lab data revealed a grade 4 thrombocytopenia **->** it is advised to report anaphylactic shock on an SAE Report Form and to report grade 4 thrombocytopenia on a separated SAE Report Form.
- Anonymized copies of relevant hospital records (e.g. discharge summary), additional lab results, list of concomitant drugs or therapies, should be provided as attachments. In addition, for fatal cases, autopsy report if available should be provided (refer also to section 3.11).

The MSF PV Unit is available for questions and further guidance on the SAE Report Form completion.

3 Detailed instructions

3.1. Administrative information

		Case number:
SERIOUS ADVERSE EVENT (SAE) REPORT FORM		
Sponsor: Médecins Sans Frontières	Protocol/Program n°:	Site n° (for studies) or country:
Initial report: ☐	Follow-up report: ☐	Date of report: ____ / _____ / _____ (dd/Mmm/yyyy)

For CTs, protocol and site numbers should be informed. For other programs, the program number or name, as well as the country of occurrence of the event should be entered.

When transmitting information on an SAE for the first time, the box 'initial report' should be ticked, when reporting supplementary information on an SAE previously transmitted, 'follow-up report' should be selected.

'Date of report' field title is self-explanatory.

The field 'Case number' is available to capture the number of the case attributed by MSF PV unit; at time of initial reporting this field should be left blank.

3.2. Patient information

Patient information					
Patient n°:	Initials:	Date of birth: ____ / _____ / _____ (dd/Mmm/yyyy)	Gender: F ☐ M ☐	Height: ..... cm	Weight: ..... kg

For CTs and programs where patients are allocated an alpha-numeric identifier, the appropriate field ('Patient n°') should be populated with this information. All information about the patient must be anonymized. Other fields' titles are self-explanatory.

3.3. Serious adverse event(s) information

	Serious adverse event(s) information		SAE 1	SAE 2	SAE 3
1	Adverse event term		.....	.....	.....
1	Event onset date (dd/Mmm/yyyy)		___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
1	Date event became serious (dd/Mmm/yyyy)		___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
1	Event end date (dd/Mmm/yyyy)		___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
1	Duration if <1 day (hrs/min)		___ / ____	___ / ____	___ / ____
2	Seriousness criteria	Death	☐	☐	☐
2			*In case of death:*	Death date: ____ / _____ / _____	Autopsy: Yes ☐ No ☐
2		Life-threatening	☐	☐	☐
2		Hospitalization required / prolonged	☐	☐	☐
2			*Hospitalization dates:*	Admission: ____ / _____ / _____	Discharge: ____ / _____ / _____
2		Persistent or significant disability / incapacity	☐	☐	☐
2		Congenital anomaly / birth defect	☐	☐	☐
2		Otherwise medically important	☐	☐	☐
2	Non-serious reportable information		☐	☐	☐
3	Severity		Grade 1 ☐ 2☐ 3☐ 4☐	Grade 1 ☐ 2☐ 3☐ 4☐	Grade 1 ☐ 2☐ 3☐ 4☐
4	Event outcome	Fatal	☐	☐	☐
4		Not resolved	☐	☐	☐
4		Resolved	☐	☐	☐
4		Resolved with sequelae	☐	☐	☐
4		Resolving	☐	☐	☐
4		Unknown	☐	☐	☐

1. Up to 3 SAEs can be entered, if more SAEs have to be reported, the page can be re-printed with the mention 'Supplemental page' and incremented numbering 'SAE 4, 5, 6' added manually. If all signs and symptoms experienced by a patient can be grouped under a single diagnosis, diagnosis should be reported as 'Adverse event term' and signs/symptoms only reported under 'Event description' (section 3.6). In the situations, where diagnosis is not feasible at time of reporting, signs and symptoms should be listed as 'Adverse event term'.

- The numbering (SAE 1, SAE 2, SAE 3) allows for causality assessment in section 3.5.
- Adverse event term for cases of overdose should be 'Overdose of [Drug name]'.
- Date of onset, date the event became serious and date of resolution of the event should be documented.
  - If the event is ongoing at time of reporting, the event end date should be left blank.
  - Onset date and date the event became serious can be similar or different, e.g. fever grade 2 starting on 03-Apr-2015 *[onset date]*, aggravated to grade 4 on 04-Apr-2015 *[date event became serious]* and patient was hospitalized.
- Event's duration should be populated only for the events lasting less than 1 day, e.g. anaphylactic shock for 5 minutes.

2. The seriousness criteria for each reported events should be selected as appropriate (see definition in section 1). In some trials/programs/therapeutic areas, further specifications are added; the CT protocol or the program's PV guideline should be strictly followed (e.g. in some CTs, hospitalization for elective surgery is not serious).

- In case of fatal adverse events, death date and autopsy status (yes/no) should be documented. If autopsy report is available, an anonymized copy should be provided (see section 3.11).
- Hospitalization dates should be documented; in case the patient was hospitalized several times for the same SAE, the Event description section (section 3.6) should be used to capture all admission/discharge dates.
- The Event description section (section 3.6) should additionally be used to add details such as description of the type of disability/incapacity (if applicable).
- For overdoses without associated SAEs or for other non-serious events requiring expedited reporting (e.g. AEs of special interest) as specified in CT protocol or program's PV guideline, the box 'Non-serious reportable information' needs to be selected.

3. Severity grading is mandatory for each SAE and should be performed using the available severity grading scale (from grade 1 to 4). Generally, details on the severity grading system are available in the CT protocol or program's PV guidelines.

4. Event outcome, when known, should be documented. For events considered resolved with sequelae, a description of these is expected in the Event description section (see section 3.6).

- Fatal: the event is the cause of patient's death or one of the causes of patient's death.
- Not resolved: the event is ongoing, no improvement is observed.
- Resolved: the event is fully resolved or stabilized; return to baseline condition for chronic disorders.
- Resolved with sequelae: the event is resolved, but patient has some permanent condition as a consequence of the event (e.g. mild paraesthesia following transient ischaemic attack).
- Resolving: the event is improving, lab results returned improved results, patient's general condition is better but not fully resolved/stabilized or returned to baseline condition.
- Unknown: the reporter has no information on the event's outcome.

3.4. Suspected drugs

	Suspected drug(s)	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
1	Suspected drug name (INN)	.....	.....	.....	.....	.....	.....	.....
	Daily dose & route							
	Batch number							
	Treatment start date (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Treatment stop date (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
2	Action taken in response to the event							
	Dose maintained	☐	☐	☐	☐	☐	☐	☐
	Dose reduced	☐	☐	☐	☐	☐	☐	☐
	New daily dose							
	On (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Drug permanently withdrawn	☐	☐	☐	☐	☐	☐	☐
	On (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Drug interrupted	☐	☐	☐	☐	☐	☐	☐
	From (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	To (dd/MMm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Not applicable	☐	☐	☐	☐	☐	☐	☐
3	Event diminished after drug stopped/dose reduced?	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐
	Event reappeared after drug/dose reintroduction?	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐

1. Up to 7 suspected drugs can be entered, if more suspected drugs have to be reported, the page can be re-printed with the mention 'Supplemental page' and incremented numbering 'Drug 8, 9, 10, etc.' added manually. Information on each drug including the International Non-proprietary Name (INN - preferred) (or trade name/active substance), daily dose, route of administration, batch number and administration dates should be mentioned.

- The numbering (Drug 1, Drug 2, Drug 3, etc.) allows for causality assessment in section 3.5.
- As a convention, in a CT, at least all study drugs (including Standard of Care drugs) are to be considered suspected drugs. In the post-marketing setting, medical judgment should apply when selecting suspected drugs. As a general rule, in a tuberculosis (TB) program, at least all ongoing TB treatments administered at time of event should be suspected. Other 'non-suspected' drugs can be recorded as concomitant medications (see section 3.8) or as past drugs (see section 3.9).
- In case of drug-drug interaction (DDI), all interacting drugs have to be recorded as suspected and the potential/proven DDI mentioned in the Event description section of the SAE Report Form (see section 3.6).

2. Action taken following the occurrence of the SAE(s) should be documented for each drug using the possibilities presented in the table. Action taken is considered not applicable, if the drug was already stopped at time of event's first occurrence or, for example, if the event appeared pre-treatment in a patient enrolled in a CT.

3. Information on the appearance/disappearance of the symptoms following changes in drug administration (discontinuation, dose reduction, drug reintroduction, full dose reintroduction) should be documented using the tick boxes.

3.5. Causality assessment

Causality assessment	SAE 1							SAE 2							SAE 3						
Related to Drug No.	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other drugs, specify:	.....							.....							.....						
Not related to Drug No.	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other drugs, specify:	.....							.....							.....						
Other causal factors (incl. med.history, procedure, etc.)	.....							.....							.....						

The reporter (the Investigator or co-Investigator in CTs) should determine for each SAE the causal relationship with each suspected drug using the categories defined as follows:

1. **Related**: there is a reasonable possibility that the SAE may be related to the drug(s). Elements in favour of a reasonable causal relationship include (but are not limited to):
    - A favourable temporal relationship,
    - A positive dechallenge, meaning symptoms are receding when the drug(s) is withdrawn or the dose is reduced,
    - A positive rechallenge, meaning symptoms are reappearing when the drug(s) is reintroduced or the full dose is re-administered,
    - A plausible pharmacological/biological mechanism of action (whether proven or potential),
    - Previous knowledge of similar reaction with the drug(s), or
    - No other evident cause (e.g. previous disease, other drugs).
2. **Not Related**: there is **no** reasonable possibility that the SAE is related to the drug(s). This implies that there is a plausible alternative cause for the SAE that better explains the occurrence of the SAE or that highly confounds the causal relationship between the drug(s) and the SAE.

In the situations where there is insufficient information to evaluate the causal relationship, 'related' should be conservatively selected by default.

Any other causal factor including pre-existing conditions, risk factors, trial procedure, etc., should be mentioned as 'free-text'.

3.6. Event description

Event description Provide a clear description of the sequence of events, diagnosis, relevant investigation results (ECG, CT scan, etc.), corrective treatments, evolution.	

This free-text field allows for a detailed description of the relevant information on the course/sequence of events, relevant investigation results (e.g. ECG, CT scan), drugs or other therapy for the event, hospitalization dates in case of multiple admissions, description of disabilities or sequelae as a consequence of the event, and any other relevant information on the case. Internationally accepted abbreviations can be used when necessary.

3.7. Relevant laboratory tests

Relevant laboratory tests			
Test	Date (*dd/Mmm/yyyy*)	Result (unit)	Reference range
	___/ ____/ _____		
	___/ ____/ _____		
	___/ ____/ _____		
	___/ ____/ _____		

Relevant tests should be listed including test name (e.g. serum blood urea nitrogen), test date, results including units and reference range. Full lab results can be appended to the Report Form if relevant to the case (section 3.11).

3.8. Concomitant medications

Concomitant medications					
Drug name (INN)	Daily dose and route	Indication	Treatment start date (*dd/Mmm/yyyy*)	Treatment stop date (*dd/Mmm/yyyy*)	Continued
			___/ ____/ _____	___/ ____/ _____	☐ Yes ☐ No
			___/ ____/ _____	___/ ____/ _____	☐ Yes ☐ No
			___/ ____/ _____	___/ ____/ _____	☐ Yes ☐ No
			___/ ____/ _____	___/ ____/ _____	☐ Yes ☐ No
			___/ ____/ _____	___/ ____/ _____	☐ Yes ☐ No

This section aims at capturing all relevant concomitant drugs, including herbals/complements or self-medications. Suspected drugs should be exclusively entered in the dedicated field (see section 3.4), drugs used to treat the event should be entered in Event description (see section 3.6), and past drugs, i.e. those stopped before the start of the TB treatment and other suspected drugs, in the medical history field (see section 3.9).

3.9. Medical history

Relevant medical history Indicate relevant medical history, including prior diagnoses, past laboratory investigations, X-ray, ECG prior to treatment, previous procedures, and relevant past drugs.	

Relevant medical history should include a list of selected prior medical diagnoses, risk factors, prior lab or investigation results (e.g. abnormal sinus rhythm 6 months prior to TB drug start), relevant familial history (e.g. family history of cancer), social circumstances (e.g. ongoing divorce, leaving in a slum area), habits (e.g. alcohol use, drug abuse), past drugs, and any other relevant information to the case. Internationally accepted abbreviations can be used when necessary.

3.10. Reporter information

Reporter				
Name of reporter:	Role in trial/program:	Date of event's awareness: *ALL SAEs to be reported within 24 hrs of awareness* ___/ ____/ _____	Address: Email: Phone:	Date and signature: ___/ ____/ _____

Titles in this section are self-explanatory. The SAE awareness date is crucial for proper expedited reporting to the relevant stakeholders (e.g. Health Authorities), if appropriate. For CTs, the Investigator or co-Investigator is responsible to approve and sign the SAE Report Form. In post-marketing programs, the relevant function (physician, nurse, etc.) should sign the form as per program's PV guideline.

3.11. Case status and annexes

Further information on this SAE expected?	**Yes** ☐ **No** ☐ *If yes please send a follow-up report once new information is available*	**Any annex to this document?** (e.g. discharge summary, autopsy report, lab results)	**Yes** ☐ **No** ☐ *If yes, list the annexes:*

The reporter is expected to pro-actively inform on the possibility of getting additional information on the case. If this information is not known at time of reporting, this field can be left blank.

Any annex to the SAE Report Form such as anonymised discharge summary, lab results, or autopsy reports, should be listed to ensure proper receipt check at MSF PV Unit.

4 Special situation – Parent/Child Foetus reports

In the situations where a female patient exposed in the frame of CT or a program is found to be pregnant, a Pregnancy Report Form should be populated and transmitted to MSF PV Unit. This is also the applicable process for a pregnancy in the female partner of a male patient exposed in the frame of a CT/program.

In addition, any SAE occurring in the mother or the foetus/child has to be recorded and transmitted to MSF PV Unit using an SAE Report Form.

- In the event of an SAE in the mother (e.g. late miscarriage), the SAE Report Form should mention the mother as the patient (section 3.2) and the serious mother's event (e.g. late miscarriage) as the SAE (section 3.3). In addition, a Pregnancy Report Form captures all pregnancy information (see Pregnancy Report Form completion guidelines).
- In the event of an SAE in the foetus/child (e.g. spina bifida), the SAE Report Form should mention the foetus/child as the patient (section 3.2) and the serious foetus/child event (e.g. spina bifida) as the SAE (section 3.3). In addition, a Pregnancy Report Form captures all pregnancy information (see Pregnancy Report Form completion guidelines).
- If both the mother and the foetus/child experienced SAEs (e.g. vaginal haemorrhage and foetal distress), 2 SAE Report Forms should be completed (1 for vaginal haemorrhage in the mother and 1 for foetal distress in the baby), as well as 1 Pregnancy Report Form that captures all pregnancy information.

5 References

ICH E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 27 October 1994.

ICH E2B(R2) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. 5 February 2001.

Question Bank

1. Describe the Adverse Event Reporting Form with schematic representation?
2. Explain the Pharmacovigilance centers in India?
3. Write an essay on the function and importance of Uppasla Monitoring Center?

References

1. A Handbook of Bioanalysis and Drug Metabolism by Gary Evans.
2. Clinical trial risk management by Martin Robinson & Simon Cook.
3. Clinical Trials: A Practical Guide to Design, Analysis & Reporting by Duolao Wang & Ameet Bakhai.
4. Data Monitoring committees in Clinical Trials Ebook by Susan S Ellenberg, Thomas R Flemming, David L Demets.
5. Drug Safety Evaluation by Shayne C Gad.
6. Guideline for Drug Regulatory Submissions by Sandy Weiberg.
7. Handbook of Bioequivalence testing by Sarfaraz K. Niazi.

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UNIT – V - Periodic safety update reports (PSUR) for marketed drugs – SMB5401

Periodic safety update report

VII.A. Introduction

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

The legal requirements for submission of PSURs are established in Regulation (EC) No 726/2004, Directive 2001/83/EC and in the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (hereinafter referred to as IR). All applicable legal requirements in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

The format of PSURs shall follow the structure described in the IR Article 35. This Module provides guidance on the preparation, submission and assessment of PSURs.

The scope, objectives, format and content of the PSUR are described in VII.B.. The required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)). The PBRER format replaces the PSUR format previously described in the ICH-E2C(R1). In line with the EU legislation, the report is described as PSUR in the GVP Modules.

Further details and guidance for the submission of PSURs in the EU, including the list of Union references dates and frequency of submission are provided in VII.C., which also covers the single EU assessment of PSURs in VII.C.4.. Details related to the quality system are provided in VII.C.6. and the publication of PSUR-related documents in VII.C.7. as transparency provisions.

Each marketing authorisation holder shall be responsible for submitting PSURs for its own products [DIR Art 107b] [REG Art 28 (2)] and should submit PSURs to the Agency (see VII.C.9. for transitional arrangements) according to the following timelines:

- within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs requested by competent authorities will normally be specified in the request, otherwise the ad hoc PSURs should be submitted within

90 calendar days of the data lock point.

It should be noted that detailed listings of individual cases shall not be included systematically [IR Art 34(4)]. The PSUR should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.

Recital 23 of Directive 2010/84/EU states that the obligations imposed in respect of PSURs should be proportionate to the risks posed by medicinal products. PSUR reporting should therefore be linked to the risk management systems of a medicinal product (see Module V). The "modular approach" of the PSUR described in VII.B.5. aims to minimise duplication and improve efficiency during the preparation and review of PSURs along with other regulatory documents such as the development safety update report (DSUR)[1] or the safety specification in the Risk Management Plan (RMP), by enabling the common content of particular sections where appropriate to be utilised interchangeably across different PSURs, DSURs and RMPs.

The amended Directive 2001/83/EC also waives the obligation to submit PSURs routinely for generic medicinal products (authorised under DIR Art 10(1)), well-established use medicinal products (authorised under DIR Art 10a), homeopathic medicinal products (authorised under DIR Art 14) and traditional herbal medicinal products (authorised under DIR Art 16a), [DIR Art 107b(3)]. For such products, PSURs shall be submitted where there is a condition in the marketing authorisation or when requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active substance after its authorisation [DIR Art 107b(3)(a) and (3)(b)].

Competent authorities in the Member States shall assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products [DIR Art 107d].

In order to increase the shared use of resources between competent authorities in Member States, a single assessment of PSURs should be performed in the EU for different medicinal products containing the same active substance or the same combination of active substances authorised in more than one Member State for which a Union reference date and frequency of submission of PSURs has been established. The EU single assessment can include joint assessment for medicinal products authorised through either national or centralised procedures for marketing authorisation. The Agency shall make available a list of Union reference dates and frequency of submission [REG Art 26(g)] which will be legally binding.

As part of the assessment, it should be considered whether further investigations need to be carried out and whether any action concerning the marketing authorisations of products containing the same active substance or the same combination of active substances, and their product information is necessary.

The Agency shall make the PSURs available to the competent authorities in Member States, members of the Pharmacovigilance Risk Assessment Committee (PRAC), of the Committee for Medicinal Products for Human use (CHMP) and of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and the European Commission by means of a PSUR repository [DIR Art 107b(2)].

VII.B. Structures and processes

VII.B.1. Objectives of the periodic update safety report (PSUR)

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

For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trials. A different risk-benefit balance may emerge as pharmacovigilance reveals further information about safety. The marketing authorisation holder should therefore re- evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance (see Module XII) and risk management (see Module V) to facilitate optimisation of the risk-benefit balance through effective risk minimisation.

Urgent safety information should be reported through the appropriate mechanism. A PSUR is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide the means by which new safety issues are detected, (see Module IX and XII). It is acknowledged that the review of the data in the PSUR may lead to new safety issues being identified.

VII.B.2. Principles for the evaluation of the risk-benefit balance within PSURs and scope of the information to be included

Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimisation.

After a marketing authorisation is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long term use, to confirm that the risk-benefit

balance remains favourable.

The analysis of the risk-benefit balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available[2], with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.

The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorised indications and use which is not in line with the product information. If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation data, information from spontaneous reports and publications in the literature.

The scope of the benefit information should include both clinical trial and real world data in authorised indications.

The integrated benefit-risk evaluation should be performed for all authorised indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorised indications).

The evaluation should involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.

2. Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the medicinal product.

3. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information. Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation actions that are planned to be implemented.

4. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

VII.B.3. Principles for the preparation of PSURs

Unless otherwise specified by competent authorities, the marketing authorisation holder shall prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorised indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly [IR Art 34(6)]. There might be exceptional scenarios where the preparation of separate PSURs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the relevant competent authorities preferably at the time of authorisation.

Case narratives shall be provided in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern [IR Art 34(4)]. In this context, the term "case narratives" refers to clinical evaluations of individual cases rather than the CIOMS narratives. It should not be necessary to provide the actual CIOMS narrative text included in the individual case safety report (ICSR) but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal.

When data received at the marketing authorisation holder from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorisation holder's product information, these data should be included and discussed in the PSUR.

The format and table of contents of all PSURs shall be as described in the IR Art 35 and each report should include interval as well as cumulative data. As the PSUR should be a single stand–alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

The GVP Modules on Product- or Population-Specific Considerations[3] should be consulted as applicable when preparing a PSUR.

VII.B.4. Reference information

Risk minimisation activities evaluated in the PSUR include updates to the product information.

The reference product information for the PSUR should include "core safety" and "authorised indications" components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PSUR, the reference product information

document should list all authorised indications in ICH countries[4] or regions. When the PSUR is also submitted to other countries in which there are additional locally authorised indications, these indications may be either added to the reference product information or handled as a regional appendix as considered most appropriate by the marketing authorization holder. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarised in the PSUR section 17.1 ("Important baseline efficacy and effectiveness information"). Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.

The following possible options can be considered by the marketing authorisation holders when selecting the most appropriate reference product information for a PSUR:

- Company core data sheet (CCDS)

– It is common practice for marketing authorisation holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorised indications for which benefit is evaluated.

– When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR.

- Other options for the reference product information

– When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one country or region, or for established/generics products on the market for many years), the marketing authorisation holder should clearly specify the reference information being used. This may comprise national or regional product information such as the EU summary of product characteristics (SmPC).

– Where the reference information for the authorised indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR (see VII.B.5.20.).

The marketing authorisation holder should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety

information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PSUR section 4 ("Changes to the reference safety information") and where relevant, discussed in PSUR section 16 ("Signal and risk evaluation"). These changes may include:

- changes to contraindications, warnings/precautions sections;
- addition to adverse reactions and interactions;
- addition of important new information on use in overdose; and
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

The marketing authorisation holder should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) as an appendix to the PSUR (see VII.B.5.20.). The reference product information should be dated and version controlled.

Where new information on safety that could warrant changes to the authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section 14 ("Late-breaking information"), if feasible. If stipulated by applicable regional requirements, the marketing authorisation holder should provide, in the regional appendix, information on any final, ongoing and proposed changes to the national or local authorised product information (see VII.C.5.)

VII.B.5. Format and contents of the PSUR

The PSUR shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last PSUR [IR Art 34(1)]. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment.

Because clinical development of a medicinal product frequently continues following marketing authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate.

The PSUR shall provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the

marketing authorisation [DIR Art 107b(1)(a)].

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:

- non-clinical studies;
- spontaneous reports (e.g. on the marketing authorisation holder's safety database);
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilisation information;
- clinical trials, including research in unauthorised indications or populations;
- observational studies, including registries;
- patient support programs;
- systematic reviews and meta-analysis;
- marketing authorisation holders sponsored websites[5];
- published scientific literature or reports from abstracts, including information presented at scientific meetings;
- unpublished manuscripts;
- licensing partners, other sponsors or academic institutions and research networks;
- competent authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorisation holder to present safety, efficacy and effectiveness information in the PSUR and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the marketing authorisation holder, a list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.

A PSUR shall be prepared following the full modular structure set out in Annex II of the IR [IR Art 35].

For the purposes of this Module, sources of information include data regarding the active substance(s) included in the medicinal product, or the medicinal product that the marketing

authorisation holder may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or risk-benefit balance. It is therefore recognised that while the same format (as defined in the IR) shall be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the marketing authorisation holder. For example, for a marketing authorisation holder sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the marketing authorisation holder, only the published report may be accessible.

The level of detail provided in certain sections of the PSUR should depend on known or emerging important information on the medicinal product's benefits and risks. This approach is applicable to those sections of the PSUR in which there is evaluation of information about safety, efficacy, effectiveness, safety signals and risk-benefit balance.

When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on PBRER should also be applied. Guidance on the titles, order and content of the PSUR sections is provided in VII.B.5.1. to VII.B.5.21.. When no relevant information is available for any of the sections, this should be stated.

- Part I: Title page including signature[6]
- Part II: Executive Summary
- Part III: Table of Contents

1. Introduction
2. Worldwide marketing authorisation status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns

5.1. Cumulative subject exposure in clinical trials

5.2. Cumulative and interval patient exposure from marketing experience

6. Data in summary tabulations

6.1. Reference information

6.2. Cumulative summary tabulations of serious adverse events from clinical trials

6.3. Cumulative and interval summary tabulations from post-marketing data sources

7. Summaries of significant findings from clinical trials during the reporting interval

7.1. Completed clinical trials

7.2. Ongoing clinical trials

7.3. Long-term follow-up

7.4. Other therapeutic use of medicinal product.

7.5. New safety data related to fixed combination therapies

8. Findings from non-interventional studies

9. Information from other clinical trials and sources

9.1. Other clinical trials

9.2. Medication errors

10. Non-clinical Data

11. Literature

12. Other periodic reports

13. Lack of efficacy in controlled clinical trials

14. Late-breaking information

15. Overview of signals: new, ongoing or closed

16. Signal and risk evaluation

16.1. Summaries of safety concerns

16.2. Signal evaluation

16.3. Evaluation of risks and new information

16.4. Characterisation of risks

16.5. Effectiveness of risk minimisation (if applicable)

17. Benefit evaluation

17.1. Important baseline efficacy and effectiveness information

17.2. Newly identified information on efficacy and effectiveness

17.3. Characterisation of benefits

18. Integrated benefit-risk analysis for authorised indications

18.1. Benefit-risk context – Medical need and important alternatives

18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the PSUR

PSUR title page

The title page should include the name of the medicinal product(s)[7] and substance, international birth date (IBD) (the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world), reporting interval, date of the report, marketing authorisation holder details and statement of confidentiality of the information included in the PSUR.

The title page shall also contain the signature. PSUR executive summary

An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR and should contain the following information:

- introduction and reporting interval;
- medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
- estimated cumulative clinical trials exposure;
- estimated interval and cumulative exposure from marketing experience;
- number of countries in which the medicinal product is authorised;
- summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk analysis evaluation” of the PSUR);

- actions taken and proposed for safety reasons, (e.g. significant changes to the reference product information, or other risk minimisation activities);
- conclusions.

PSUR table of contents

The executive summary should be followed by the table of contents.

VII.B.5.1. PSUR section "Introduction"

The marketing authorisation holder should briefly introduce the product(s) so that the PSUR "stands alone" but it is also placed in perspective relative to previous PSURs and circumstances. The introduction should contain the following information:

- IBD, and reporting interval;
- medicinal product(s), therapeutic class(es), mechanism(s) of action, authorised indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
- a brief description of the population(s) being treated and studied;

VII.B.5.2. PSUR section "Worldwide marketing authorisation status"

This section of the PSUR should contain a brief narrative overview including: date of the first authorisation worldwide, indications(s), authorised dose(s), and where authorised.

VII.B.5.3. PSUR section "Actions taken in the reporting interval for safety reasons"

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

- a significant influence on the risk-benefit balance of the authorised medicinal product; and/or

- an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

If known, the reason for each action should be provided and any additional relevant information should be included as appropriate. Relevant updates to previous actions should also be summarised in this section.

Examples of significant actions taken for safety reasons include: Actions related to investigational uses:

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial[8] or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- recall of investigational drug or comparator;
- failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a marketing authorisation application;
- risk management activities, including:

– protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);

– restrictions in study population or indications;

– changes to the informed consent document relating to safety concerns;

– formulation changes;

– addition by regulators of a special safety-related reporting requirement;

– issuance of a communication to investigators or healthcare professionals; and

– plans for new studies to address safety concerns.

Actions related to marketing experience:

- failure to obtain or apply for a marketing authorisation renewal;
- withdrawal or suspension of a marketing authorisation;
- actions taken due to product defects and quality issues;

- suspension of supply by the marketing authorisation holder;
- risk management activities including:

– significant restrictions on distribution or introduction of other risk minimisation measures;

– significant safety-related changes in labelling documents including restrictions on use or population treated;

– communications to health care professionals; and

– new post-marketing study requirement(s) imposed by competent authorities.

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[8]"Partial suspension" might include several actions (e.g. suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses). ICH-E2C(R2) guideline (see Annex IV).

VII.B.5.4. PSUR section "Changes to reference safety information"

This PSUR section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR.

VII.B.5.5. PSUR section "Estimated exposure and use patterns"

PSURs shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorisation holder, including the results of observational or drug utilisation studies [IR Art 34 (2)].

This PSUR section should provide estimates of the size and nature of the population exposed to the medicinal product including a brief description of the method(s) used to estimate the subject/patient exposure and the limitations of that method.

Consistent methods for calculating subject/patient exposure should be used across PSURs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR introducing the change and any important difference between the results using the two methods should be highlighted.

VII.B.5.5.1. PSUR sub-section "Cumulative subject exposure in clinical trials"

This section of the PSUR should contain the following information on the patients studied in clinical trials sponsored by the marketing authorisation holder, if applicable presented in tabular formats:

- cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for "old products", detailed data might not be available;
- more detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme);
- important differences among trials in dose, routes of administration, or patient populations

can be noted in the tables, if applicable, or separate tables can be considered;

- if clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;

- when there are substantial differences in time of exposure between subjects randomised to the investigational medicinal 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);

- investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;

- if the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;

- for individual trials of particular importance, demographic characteristics should be provided separately.

Examples of tabular format for the estimated exposure in clinical trials are presented in VII. Appendix 1, Tables VII.2, VII.3 and VII.4.

VII.B.5.5.2. PSUR sub-section "Cumulative and interval patient exposure from marketing experience"

Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR). Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data should be presented according to the following categories:

1. Post-authorisation (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. Post-authorisation use in special populations:

Where post-authorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include for instance non-interventional studies designed to obtain this information, including registries. Other sources of information may include data collection outside a study environment including information collected through spontaneous reporting systems (e.g. information on reports of pregnancy exposure without an associated adverse event may be summarised in this section). Populations to be considered for discussion include, but might not be limited to:

- paediatric population;
- elderly population;
- pregnant or lactating women;
- patients with hepatic and/or renal impairment;
- patients with other relevant co-morbidity;
- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- populations with specific racial and/or ethnic origins.

3. Other post-authorisation use:

If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti- epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns

of use without reference to adverse reactions should be summarised in this section as applicable. Such information may be received via spontaneous reporting systems, medical information queries, customer's complaints, screening of digital media or via other information sources available to the marketing authorisation holder. If quantitative information on use is available, it should be provided.

If known, the marketing authorisation holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information may be linked to clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorisation holder should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR (e.g. authorised indication, route of administration, contraindications).

Signals or risks identified from any data or information source should be presented and evaluated in the relevant sections of the PSUR.

Examples of tabular format for the estimated exposure from marketing experience are presented in VII. Appendix 1, Tables VII.5 and VII.6.

VII.B.5.6. PSUR section "Data in summary tabulations"

The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non- interventional solicited source. At the discretion of the marketing authorisation holder graphical displays can be used to illustrate specific aspects of the data when useful to enhanceunderstanding.

When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations.

The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH- E2A[9] (see Annex IV). When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSURs.

VII.B.5.6.1. PSUR sub-section "Reference information"

This sub-section of the PSUR should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

VII.B.5.6.2. PSUR sub-section "Cumulative summary tabulations of serious adverse events from clinical trials"

This PSUR sub-section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorisation holder's clinical trials, from the DIBD to the data lock point of the current PSUR. The marketing authorisation holder should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational 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, data can be presented by trial, indication, route of administration or other variables.

This sub-section should not serve to provide analyses or conclusions based on the serious adverse events.

The following points should be considered:

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.

- In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.

- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and marketing authorisation holders should not unblind data for the specific purpose of preparing the PSUR.

- Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database

because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

An example of summary tabulation of serious adverse events from clinical trials can be found in VII. Appendix 1 Table VII.7.

VII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post- marketing data sources"

This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies[10]. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.

As described in ICH-E2D[11] (see Annex IV) guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.

Analysis or conclusions based on the summary tabulations should not be provided in this PSUR sub- section.

An example of summary tabulations of adverse drug reactions from post-marketing data sources can be found in VII. Appendix 1 Table VII.8.

VII.B.5.7. PSUR section "Summaries of significant findings from clinical trials during the reporting interval"

This PSUR section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the marketing authorisation holder's sponsored clinical trials during the reporting interval, from the sources specified in the sub-sections listed below. When possible and relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and region should be presented.

Signals arising from clinical trial sources should be tabulated in PSUR section 15 ("Overview on signals: new, ongoing or closed"). Evaluation of the signals, whether or not categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR section 16.2 ("Signal evaluation"). New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in PSUR sections 16.3 ("Evaluation of risks and new information") and 16.4 ("Characterisation of risks") respectively.

Findings from clinical trials not sponsored by the marketing authorisation holder should be described in the relevant sections of the PSUR.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in authorised indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness should be summarised in section 13 ("Lack of efficacy in controlled clinical trials") (VII.B.5.13).

Information from other clinical trials/study sources should be included in the PSUR sub-section 9.1 ("other clinical trials") (VII.B.5.9.1).

In addition, the marketing authorisation holder should include an appendix listing the sponsored post- authorisation interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval. The listing should include the following information for each trial:

- study ID (e.g. protocol number or other identifier);
- study title (abbreviated study title, if applicable);
- study type (e.g. randomised clinical trial, cohort study, case-control study);
- population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);
- study start (as defined by the marketing authorisation holder) and projected completion dates;
- status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

VII.B.5.7.1. PSUR sub-section "Completed clinical trials"

This sub-section of the PSUR should provide a brief summary of clinically important emerging

efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis[12]. It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

VII.B.5.7.2. PSUR sub-section "Ongoing clinical trials"

If the marketing authorisation holder 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 summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

VII.B.5.7.3. PSUR sub-section "Long term follow-up"

Where applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

VII.B.5.7.4. PSUR sub-section "Other therapeutic use of medicinal product"

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D[13] (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

VII.B.5.7.5. PSUR sub-section "New safety data related to fixed combination therapies"

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

- If the active substance that is the subject of the PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy.
- If the product itself is a fixed combination product, this PSUR sub-section should summarise important safety information arising from the individual components whether authorised or under development.

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.

VII.B.5.8. PSUR section "Findings from non-interventional studies"

This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-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 utilisation studies when relevant to multiple regions

The marketing authorisation holder should include an appendix listing marketing authorisation holder- sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval. (see VII.B.5.7. for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR (see VII.B.5.20. and VII.C.5.4.).

Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PSUR. As for other information sources, the marketing authorisation holder should present signals or risks identified from such information in the relevant sections of the PSUR.

VII.B.5.9. PSUR section "Information from other clinical trials and sources"

VII.B.5.9 1. PSUR sub-section "Other clinical trials"

This PSUR sub-section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

VII.B.5.9 2. PSUR sub-section "Medication errors"

This sub-section should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of

safety data or the overall benefit- risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

VII.B.5.10. PSUR section "Non-clinical data"

This PSUR section should summarise 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. Results from studies designated to address specific safety concerns should be included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR.

VII.B.5.11. PSUR section "Literature"

This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.

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

The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:

- pregnancy outcomes (including termination) with no adverse outcomes;
- use in paediatric populations;
- compassionate supply, named patient use;
- lack of efficacy;
- asymptomatic overdose, abuse or misuse;
- medication error where no adverse events occurred;
- important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class should be considered.

The publication reference should be provided in the style of the Vancouver Convention[14,15].

VII.B.5.12. PSUR section "Other periodic reports"

This PSUR section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority. In general, the marketing authorisation holder should prepare a single PSUR for a single active substance (unless otherwise specified by the competent authority); however if multiple PSURs are prepared for a single medicinal product, this section should also summarise significant findings from other PSURs if they are not presented elsewhere within the report.

When available, based on the contractual agreements, the marketing authorisation holder

should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, other marketing authorisation holders or other contractual partners).

VII.B.5.13. PSUR section "Lack of efficacy in controlled clinical trials"

This section should summarise data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute coronary syndromes) that could reflect a significant risk to the treated population.

VII.B.5.14. PSUR section "Late-breaking information"

The marketing authorisation holder should summarise in this PSUR section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the marketing authorisation holder, a data monitoring committee, or a competent authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR (e.g. a well documented case of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR (see VII.B.4.), where feasible.

The data presented in this section should also be taken into account in the evaluation of risks and new information (see VII.B.5.16.3.).

VII.B.5.15. PSUR section "Overview of signals: new, ongoing, or closed"

The general location for presentation of information on signals and risks within the PSUR is shown in figure VII.1 (see VII.B.5.21.). The purpose of this section is to provide a high level overview of signals[16] that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PSUR, a signal should be included once it has undergone the

initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorisation holder[17].It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicine/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide) (see Module IX).

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data, which is presented in section 16 ("Signal and risk evaluation") of the PSUR.

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR.

Examples of new signals would therefore include new information on a previously:

- Close and refuted signal, which would result in the signal being re-opened.
- Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well documented case report of agranulocytosis with no presence of possible alternative causes is received).
- Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section, or as an appendix the marketing authorisation holder should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:

- a brief description of the signal;
- date when the marketing authorisation holder became aware of the signal;

- status of the signal at the end of the reporting interval (close or ongoing);
- date when the signal was closed, if applicable;
- source of the signal;
- a brief summary of the key data;
- plans for further evaluation; and
- actions taken or planned.

An example of tabulation of signals can be found in VII. Appendix 2.

The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in sub-section 16.2 ("Signal evaluation") of the PSUR.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in PSUR sub-section 16.3 ("Evaluation of risks and new information").

When a competent authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR, the marketing authorisation holder should summarise the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sub-section 16.2 ("Signal evaluation").

VII.B.5.16. PSUR section "Signal and risk evaluation"

The purpose of this section of the PSUR is to provide:

- A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report (VII.B.5.16.1.).
- An evaluation of all signals closed during the reporting interval (VII.B.5.16.2.).
- An evaluation of new information with respect to previously recognised identified and potential risks (VII.B.5.16.3).
- An updated characterisation of important potential and identified risks, where applicable (VII.B.5.16.4.).
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (VII.B.5.16.5.).

A flowchart illustrating the mapping of signals and risks to specific sections/sub-sections of the PSUR can be found in VII.B.5.21..

These evaluation sub-sections should not summarise or duplicate information presented in previous sections of the PSUR but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided (see VII.B.3.).

VII.B.5.16.1. PSUR sub-section "Summary of safety concerns"

The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary[18] that is current at the start of the reporting interval of the PSUR. It should provide the following safety information:

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

The following factors should be considered when determining the importance of each risk:

- medical seriousness of the risk, including the impact on individual patients;
- its frequency, predictability, preventability, and reversibility;
- potential impact on public health (frequency; size of treated population); and
- potential for avoidance of the use of a medicinal product with a preventive benefit due to a disproportionate public perception of risk (e.g. vaccines).

For products without an existing safety specification, this section should provide information on the important identified and potential risks and missing information associated with use of the product, based on pre- and post-authorisation experience. Important identified and potential risks may include, for example:

- important adverse reactions;

- interactions with other medicinal products;
- interactions with foods and other substances; medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

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

VII.B.5.16.2. PSUR sub-section "Signal evaluation"

This sub-section of the PSUR should summarise the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this sub-section are:

1. Those signals that, following evaluation, have been refuted as "false" signals based on medical judgement and scientific evaluation of the currently available information.

2. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the marketing authorisation holder.

It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals.
- Closed signals that are categorised as important potential risks.
- Closed signals that are categorised as important identified risks.
- Closed signals that are potential risks not categorised as important.

- Closed signals that are identified risks not categorised as important.

Where applicable the evaluations of closed signals can be presented by indication or population.

The description(s) of the signal evaluations can be included in this sub-section of the PSUR or in an appendix. Each evaluation should include the following information as appropriate:

- source or trigger of the signal;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) thatwere reviewed), and analytical approaches;
- results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);

- discussion;
- conclusion.

Marketing authorisation holder's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information"

This sub-section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in sub-section 16.2 ("Signal evaluation").

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the signals tabulation (see VII.B.5.15.) and evaluated in sub- section 16.2 ("Signal evaluation"), if the signal is also closed during the reporting interval of the PSUR.

Updated information on a previously recognised risk that does not constitute a signal should be included in this sub-section. Examples includes information that confirms a potential risk as an identified risk, or information which allows any other further characterisation of a previously recognised risk.

New information can be organised as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorised as important.
4. New information on other identified risks not categorised as important.
5. Update on missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in sub-section 16.4 ("Characterisation of risks") of the report. It is recommended that the level of detail of the evaluation included in this sub- section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of the new information and missing information update(s) can be included in this

sub-section of the PSUR, or in an appendix. Each evaluation should include the following information as appropriate:

- source of the new information;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the risk evaluation;
- discussion;
- conclusion, including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in sub-section 16.4 ("Characterisation of risks")

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this sub-section. Unresolved concerns and uncertainties should be acknowledged.

VII.B.5.16.4. PSUR sub-section "Characterisation of risks"

This sub-section should characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- frequency;
- numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk and precision of estimate;
- estimate of absolute risk and precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);

- dose, route of administration;
- duration of treatment, risk period;
- preventability (i.e. predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PSURs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- risks relating to the active substance;
- risks related to a specific formulation or route of administration (including occupational exposure);
- risks relating to a specific population; and
- risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

VII.B.5.16.5. PSUR sub-section: "Effectiveness of risk minimisation (if applicable)"

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

The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment [IR Art 34(3)].

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this sub-section of the PSUR.

Insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarised by region, if applicable and relevant.

When required for reporting in a PSUR, results of evaluations that became available during the reporting interval, which refer to an individual region should be provided in the PSUR regional appendix (see VII.B.5.20. and VII.C.5.5.).

VII.B.5.17. PSUR section "Benefit evaluation"

PSUR sub-sections 17.1 ("Important baseline efficacy and effectiveness information") and 17.2 ("Newly identified information on efficacy and effectiveness") provide the baseline and newly identified benefit information that support the characterisation of benefit described in sub-section 17.3 ("Characterisation of benefits") that in turn supports the benefit-risk evaluation in section 18 ("Integrated benefit-risk analysis for authorised indications").

VII.B.5.17.1. PSUR sub-section "Important baseline efficacy and effectiveness information"

This sub-section of the PSUR summarises information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information should relate to authorised indication(s) of the medicinal product listed in the reference product information (See VII.B.4.).

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.

The level of detail provided in this sub-section should be sufficient to support the characterisation of benefit in the PSUR sub-section 17.3 ("Characterisation of benefits") and the benefit-risk assessment in section 18 ("Integrated benefit-risk analysis for authorised indications").

VII.B.5.17.2. PSUR sub-section "Newly identified information on efficacy and effectiveness"

For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this sub- section of the PSUR. For authorised indications, new information on efficacy and effectiveness under conditions of actual use should also be described in this sub-section, if available. New information on efficacy and effectiveness in uses other than the authorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised indications.

Information on indications newly authorised during the reporting interval should also be included in this sub-section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in sub-section 17.3 ("Characterisation of benefits") and the benefit-risk assessment in section 18 ("Integrated benefit-risk analysis for authorised indications").

In this sub-section, particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

VII.B.5.17.3. PSUR sub-section "Characterisation 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 authorised indications.

The level of detail provided in this sub-section should be sufficient to support the analysis of benefit- risk in section 18 ("Integrated benefit-risk analysis for authorised indications").

When there are no new relevant benefit data, this sub-section should provide a characterisation of the information in sub-section 17.1 ("Important baseline efficacy and effectiveness information").

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this sub-section should be succinct.

This sub-section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:

- a brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across

trials/studies;

- new information that challenges the validity of a surrogate endpoint, if used;
- clinical relevance of the effect size;
- generalisability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
- adequacy of characterization of dose-response;
- duration of effect;
- comparative efficacy; and
- a determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice.

VII.B.5.18. PSUR section "Integrated benefit-risk analysis for authorised indications"

The marketing authorisation holder should provide in this PSUR section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. Whereas sub-sections 16.4 ("Characterisation of risks") and 17.3 ("Characterisation of benefits") present the risks and benefits, this section should provide a critical analysis and integration of the key information in the previous sections and should not simply duplicate the benefit and risk characterisation presented in the sub- sections mentioned above.

VII.B.5.18.1. PSUR sub-section "Benefit-risk context - medical need and important alternatives"

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

VII.B.5.18.2. PSUR sub-section "Benefit-risk analysis evaluation"

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

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

- Whereas previous sections/sub-sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section/sub-sections should be carried forward for integration in the benefit-risk evaluation.

- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).

- With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalisability, 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 rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).

- With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorised indications or populations, off-label use, or misuse.

- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

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

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

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

- Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PSUR has been requested, a detailed benefit- risk analysis should be presented based on cumulative data. 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.

VII.B.5.19. PSUR section "Conclusions and actions"

A PSUR should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder should assess the need for changes to the reference product information and propose changes as appropriate.

In addition and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the risk-benefit balance for further discussion with the relevant competent authority(ies). This may include proposals for additional risk minimisation activities.

For products with a pharmacovigilance or risk management plan, the proposals should also be considered for incorporation into the pharmacovigilance plan and/or risk minimisation plan, as appropriate (see Module V).

Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved summary of product characteristics (SmPC) for the product(s) for which the PSUR is submitted [IR Art 34(5)].

Proposed changes to the reference product information should be described in this section of the PSUR. The regional appendix should include proposals for product information (SmPC and package leaflet) together with information on ongoing changes when applicable.

VII.B.5.20. Appendices to the PSUR

A PSUR should contain the following appendices as appropriate, numbered as follows:

1. Reference information (see VII.B.4.).

2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.

3. Tabular summary of safety signals (if not included in the body of the report)[19].

4. Listing of all the marketing authorisation holder-sponsored interventional and non-

interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.

5. List of the sources of information used to prepare the PSUR (when desired by the marketing authorisation holder).

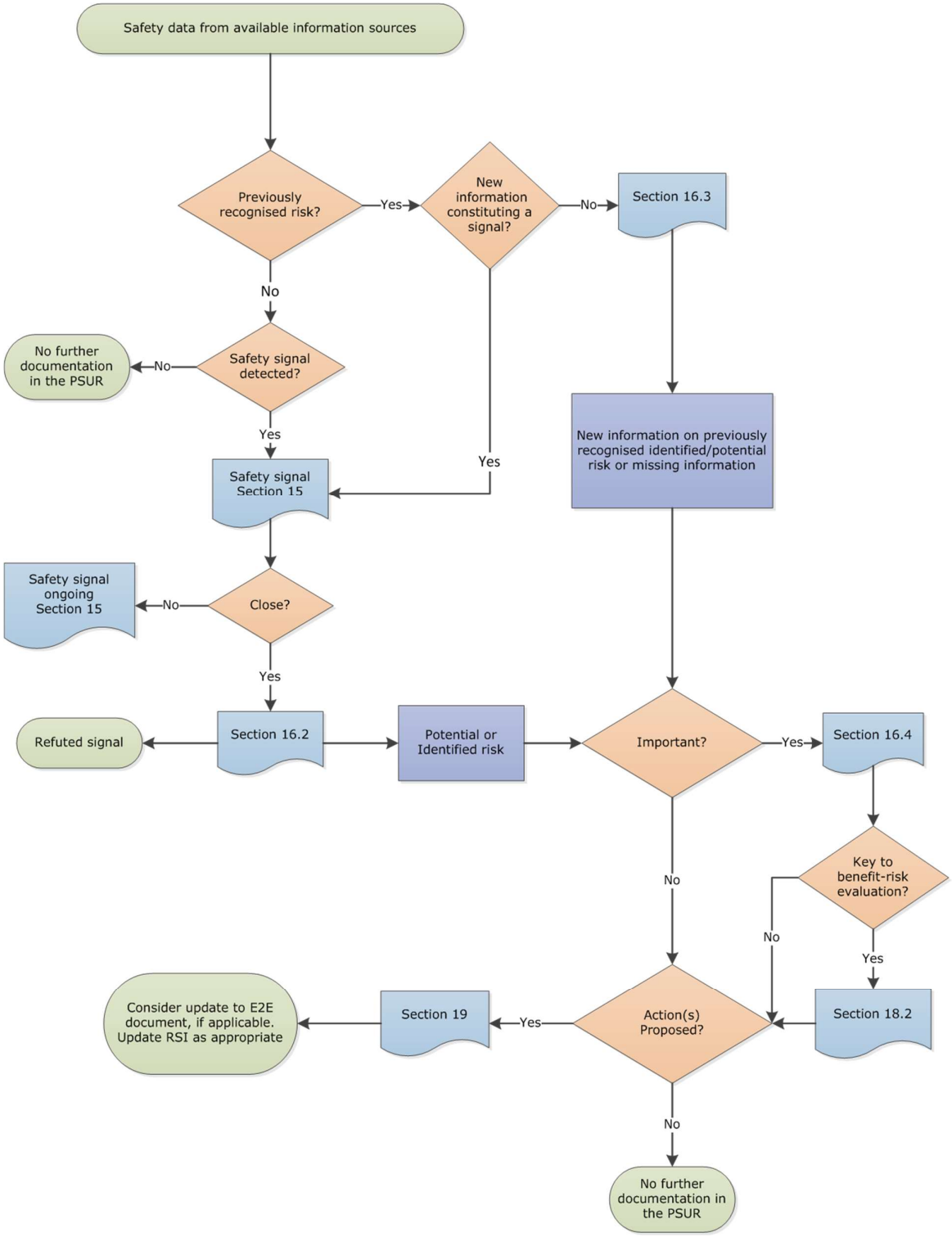
6. Regional appendix:

The requirements for the regional appendix in the EU are provided in section VII.C.5..

VII.B.5.21. Mapping signals and risks to PSUR sections/sub-sections

The following flowchart (Figure VII.1) reflects the general location for the presentation of information on signals and risks within the PSUR.

Figure VII.1. PSUR Sections/subsections – signals and risks.


Safety data from available information sources
Previously recognised risk?
Yes
New information constituting a signal?
No
Section 16.3
No
No further documentation in the PSUR
No
Safety signal detected?
Yes
Yes
Safety signal Section 15
New information on previously recognised identified/potential risk or missing information
Safety signal ongoing Section 15
No
Close?
Yes
Refuted signal
Section 16.2
Potential or Identified risk
Important?
Yes
Section 16.4
No
Key to benefit-risk evaluation?
No
Yes
Consider update to E2E document, if applicable. Update RSI as appropriate
Section 19
Yes
Action(s) Proposed?
Section 18.2
No
No further documentation in the PSUR

VII.B.6. Quality systems for PSURs at the level of marketing authorisation holders

Marketing authorisation holders should have in place structures and processes for the preparation, quality control, review and submission of PSURs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the marketing authorisation holder's quality system (see Module I).

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSURs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality system should describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PSURs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSURs. In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross departmental input to PSUR preparation.

The PSUR should also contain the assessment of specific safety issues requested by competent authorities in accordance with agreed timelines and procedures. The marketing authorisation holder should have mechanisms in place to ensure that the requests made by competent authorities during the time of their PSUR assessment are properly addressed.

The provision of the data included in the summary tabulations (see VII.B.5.6.) should undergo source data verification against the marketing authorisation holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

An appropriate quality system should be in place in order to avoid failure to comply with PSUR requirements such as:

- non-submission: complete non-submission of PSURs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the competent authorities);
- unjustified omission of information required by VII.B.5.;
- poor quality reports: poor documentation or insufficient information or evaluation

provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardised medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;

- submission of a PSUR where previous requests from competent authorities have not been addressed;
- failure to provide an explicit evaluation of the risk-benefit balance of the medicinal product;
- failure to provide adequate proposals for the local authorised product information.

Any significant deviation from the procedures relating to the preparation or submission of PSURs should be documented and the appropriate corrective and preventive action should be taken. This documentation should be available at all times.

When marketing authorisation holders are involved in contractual arrangements (e.g. licensor- licensee), respective responsibilities for preparation and submission of the PSUR to the competent authorities should be clearly specified in the written agreement.

When the preparation of the PSUR is delegated to third parties, the marketing authorisation holder should ensure that they are subject to a quality system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the marketing authorisation holder and third parties. The agreements may specifically detail the options to audit the PSUR preparation process.

VII.B.7. Training of staff members related to the PSUR process

For all organisations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSURs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and this GVP Module VII). When appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR should be in place.

Training to update knowledge and skills should also take place as necessary.

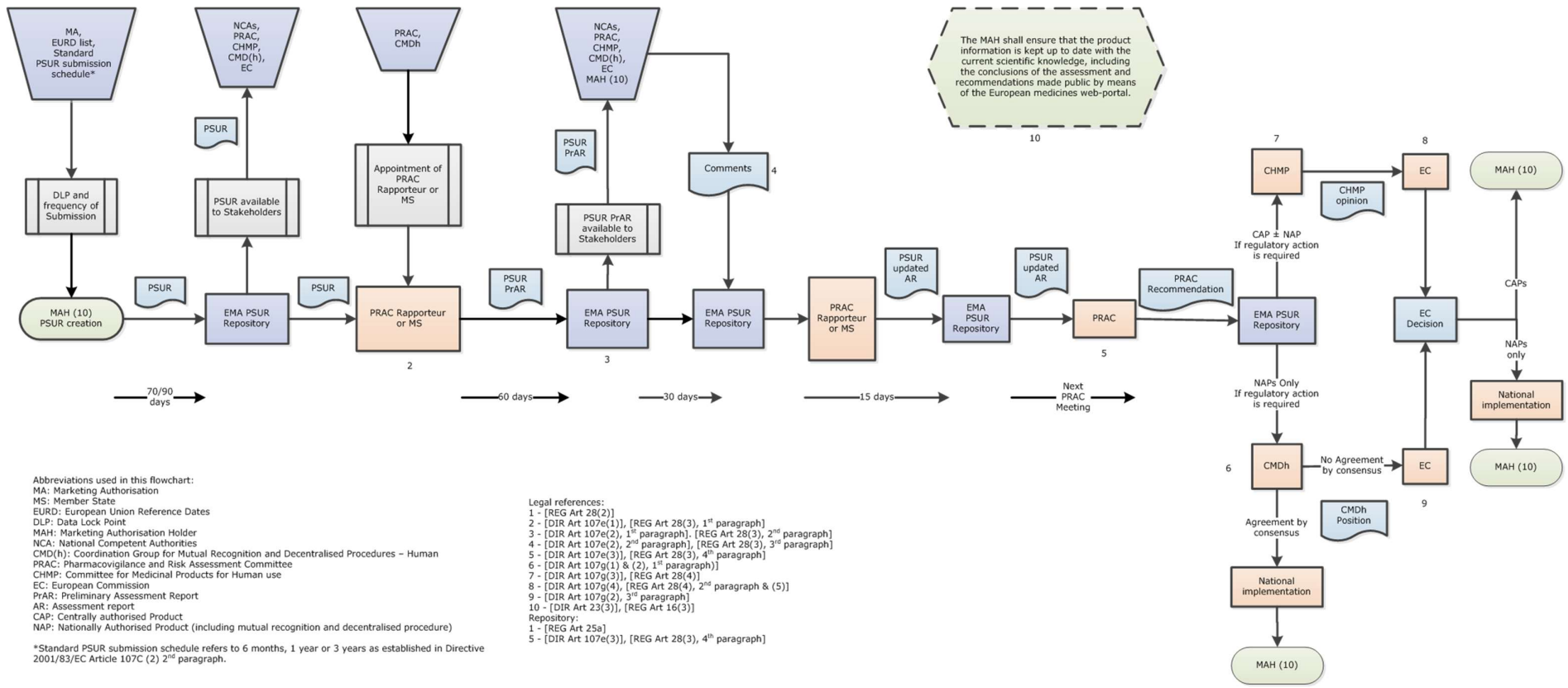
Training should cover legislation, guidelines, scientific evaluation and written procedures related to the PSUR process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

VII.C. Operation of the EU network

VII.C.1. PSUR process in the EU - General process

The following flowchart (Figure VII.2.) reflects the general process cycle for the PSUR procedure at the EU level when recommendations by the PRAC are issued. This represents a high level cycle to outline the entire process, from the preparation of the report to the implementation of the European Commission decision/national actions when applicable. Different single steps in this flowchart are formed by intermediate steps further explained and developed in different sections in this Module.

Figure VII.2. PSUR procedure - general process



Abbreviations used in this flowchart:
MA: Marketing Authorisation
MS: Member State
EURD: European Union Reference Dates
DLP: Data Lock Point
MAH: Marketing Authorisation Holder
NCA: National Competent Authorities
CMD(h): Coordination Group for Mutual Recognition and Decentralised Procedures – Human
PRAC: Pharmacovigilance and Risk Assessment Committee
CHMP: Committee for Medicinal Products for Human use
EC: European Commission
PrAR: Preliminary Assessment Report
AR: Assessment report
CAP: Centrally authorised Product
NAP: Nationally Authorised Product (including mutual recognition and decentralised procedure)

*Standard PSUR submission schedule refers to 6 months, 1 year or 3 years as established in Directive 2001/83/EC Article 107C (2) 2nd paragraph.

Legal references:
1 - [REG Art 28(2)]
2 - [DIR Art 107e(1)], [REG Art 28(3), 1st paragraph]
3 - [DIR Art 107e(2), 1st paragraph]. [REG Art 28(3), 2nd paragraph]
4 - [DIR Art 107e(2), 2nd paragraph], [REG Art 28(3), 3rd paragraph]
5 - [DIR Art 107e(3)], [REG Art 28(3), 4th paragraph]
6 - [DIR Art 107g(1) & (2), 1st paragraph)]
7 - [DIR Art 107g(3)], [REG Art 28(4)]
8 - [DIR Art 107g(4), [REG Art 28(4), 2nd paragraph & (5)]
9 - [DIR Art 107g(2), 3rd paragraph]
10 - [DIR Art 23(3)], [REG Art 16(3)]
Repository:
1 - [REG Art 25a]
5 - [DIR Art 107e(3)], [REG Art 28(3), 4th paragraph]

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY

CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES
COURSE MATERIAL

Subject Name: Pharmacovigilance and Safety monitoring **Subject Code: SMB5401**

Unit - V

VII.C.2. Standard submission schedule of PSURs

Marketing authorisation holders for products authorised before 02 July 2012 (centrally authorised products) and 21 July 2012 (nationally authorised products) and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation or determined otherwise in the list of Union reference dates, shall submit PSURs according to the following submission schedule [REG 28(2), DIR Art 107c(2)].

- at 6 months intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.

VII.C.3. List of European Union reference dates and frequency of submission of PSURs[20]

VII.C.3.1. Objectives of the EU reference dates list

The Agency shall make public a list of Union reference dates (hereinafter referred to as list of EU reference dates) and frequency of submission of PSURs by means of the European medicines web-portal [DIR Art 107c(7), REG Art 26(1)(g)].

The objectives of the list of EU reference dates and frequency of submission of PSURs are:

- Harmonisation of data lock point and frequency of submission of PSURs for the same active substance and combination of active substances:

For medicinal products containing the same active substance or combination of active substances subject to different marketing authorisations, an EU reference date should be set up and the frequency and date of submission of PSURs harmonised in order to allow the preparation of a single assessment established in DIR Art 107e(1). Such information should be included in the list published by the Agency.

- Optimisation of the management of PSURs and PSURs assessments within the EU: The list

overrules the submission schedule described in DIR Art 107c(2)(b).

For active substances or combinations of active substances included in the list, marketing authorisation holders shall vary, if applicable, the condition laid down in their marketing authorisations in order to allow the submission of PSURs in accordance to the frequency and submission date as indicated in the list [DIR 107c(4) to (7)].

The periodicity is defined on the basis of a risk-based approach in order to prioritise the periodic

re-evaluation of the risk-benefit balance of active substances in a way that best protects public health [Directive 2010/84/EU Preamble Recital 23].

- Single EU assessment and reassessment of the risk-benefit balance of an active substance based on all available safety data:

The list enables the harmonisation of PSUR submissions for medicinal products containing the same active substance or the same combination of active substances. A single EU PSUR assessment provides a mechanism for evaluating the totality of available data on the benefits and risks of an active substance or combination of active substances. The effective application of work sharing principles is important in avoiding duplication of efforts and in prioritising the use of limited resources in the best interests of European citizens.

VII.C.3.2. Description of the EU reference dates list

The Union reference date of medicinal products containing the same active substance or the same combination of active substances shall be [DIR Art 107c(5)]:

- the date of the first marketing authorisation in the EU of a medicinal product containing that active substance or that combination of active substances; or
- if the date of first marketing authorisation cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

The list of EU reference dates and frequency of submission of PSURs consists of a comprehensive list of substances and combinations of active substances in alphabetical order, for which PSURs, where required, shall be submitted in accordance with the EU reference date and the frequency as determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC) [DIR Art 107c(4) and (6)]. The list should be updated in line with the "list of all medicinal products for human use authorised in the Union" as referred to in REG Art 57(1)(b).

The EU reference dates list should contain the following information:

- the EU reference dates;
- the frequencies of submission of PSURs;
- the data lock points of the next submissions of PSURs;
- the date of publication (on the European Medicines web-portal) of the frequency for PSURs

submission and data lock point for each active substance and combination of active substances. Any change to the dates of submission and frequency on PSURs specified in the marketing authorisation shall take effect 6 months after the date of such publication [DIR Art 107c(7)].

Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU single assessment procedure (see VII.C.3.3.) such as:

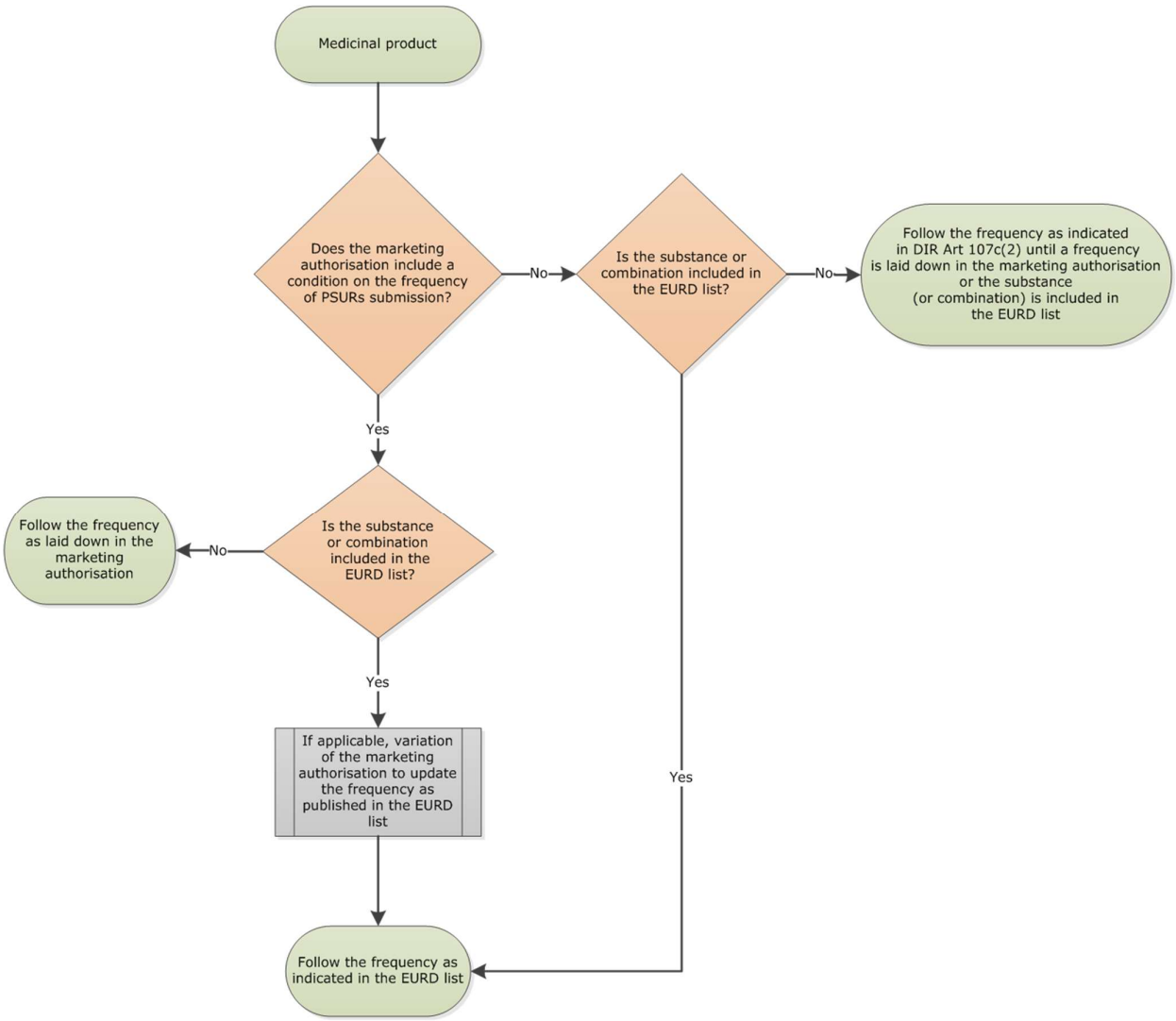
- whether or not it should cover all the indications of the substance or combination of active substances;
- whether or not it should cover all the formulations/routes of administration of the products containing a substance or combination of active substances;
- whether generic, well-established use, traditional herbal and homeopathic medicinal products shall submit a PSUR due to a request from a competent authority or due to concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted [DIR Art 107c(2) second subparagraph] (see VII.C.3.3.2.).

VII.C.3.3. Application of the list of EU reference dates to submission of PSURs

VII.C.3.3.1. Submission of PSURs for medicinal products: general requirement

Figure VII.3. presents the various potential scenarios for the submission of a PSUR as a general requirement.

Figure VII.3. Conditions for PSURs submission as general requirement



The data lock points included in the list of EU references dates enable the synchronisation of PSURs submission for products subject to different marketing authorisations and permit the EU single assessment. These data lock points are fixed on a certain date of the month, and should be used to determine the submission date (which has legal status) of the PSUR. Marketing authorisation holders can request to amend those dates in accordance with section VII.C.3.5.2.

Unless otherwise specified in the list of EU reference dates and frequency of submission, or agreed with competent authorities in Member States or the Agency, as appropriate, a single PSUR shall be prepared for all medicinal products containing the same active substance and authorised for one marketing authorisation holder. The PSUR shall cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly [IR Art 34(6)].

For medicinal products containing an active substance or a combination of active substances not included in the EU reference dates list, PSURs shall be submitted according to the PSUR frequency defined in the marketing authorisation or if not specified, in accordance with the submission schedule specified in DIR Art 107c(2) and REG Art 28(2).

VII.C.3.3.2. Submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products

By way of derogation, generics (authorised under DIR Art 10(1)), well-established use (authorised under DIR Art 10a), homeopathic (authorised under DIR Art 14) and traditional herbal (authorised under DIR Art 16a) medicinal products are exempted from submitting PSURs except in the following circumstances [DIR Art 107b(3)]:

- the marketing authorisation provides for the submission of PSURs as a condition;
- PSURs is (are) requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted (e.g. when the “reference” medicinal product is no longer marketed). The assessment reports of the requested PSURs shall be communicated to the PRAC, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the CMDh or CHMP accordingly, in order to apply the procedures laid down in DIR Art 107c(4) and 107e.

In order to facilitate and optimise the PSUR EU single assessment process, to avoid duplications of requests for PSURs and to provide transparency and predictability for the marketing

authorisation holders, the legislative provision laid down in DIR 107b(3)(b) is applied by specifying in the list of EU reference dates, the substances for which PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products are required. This specification is based on the request made by a competent authority in a Member State during the creation or maintenance of the list of EU reference dates and on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance.

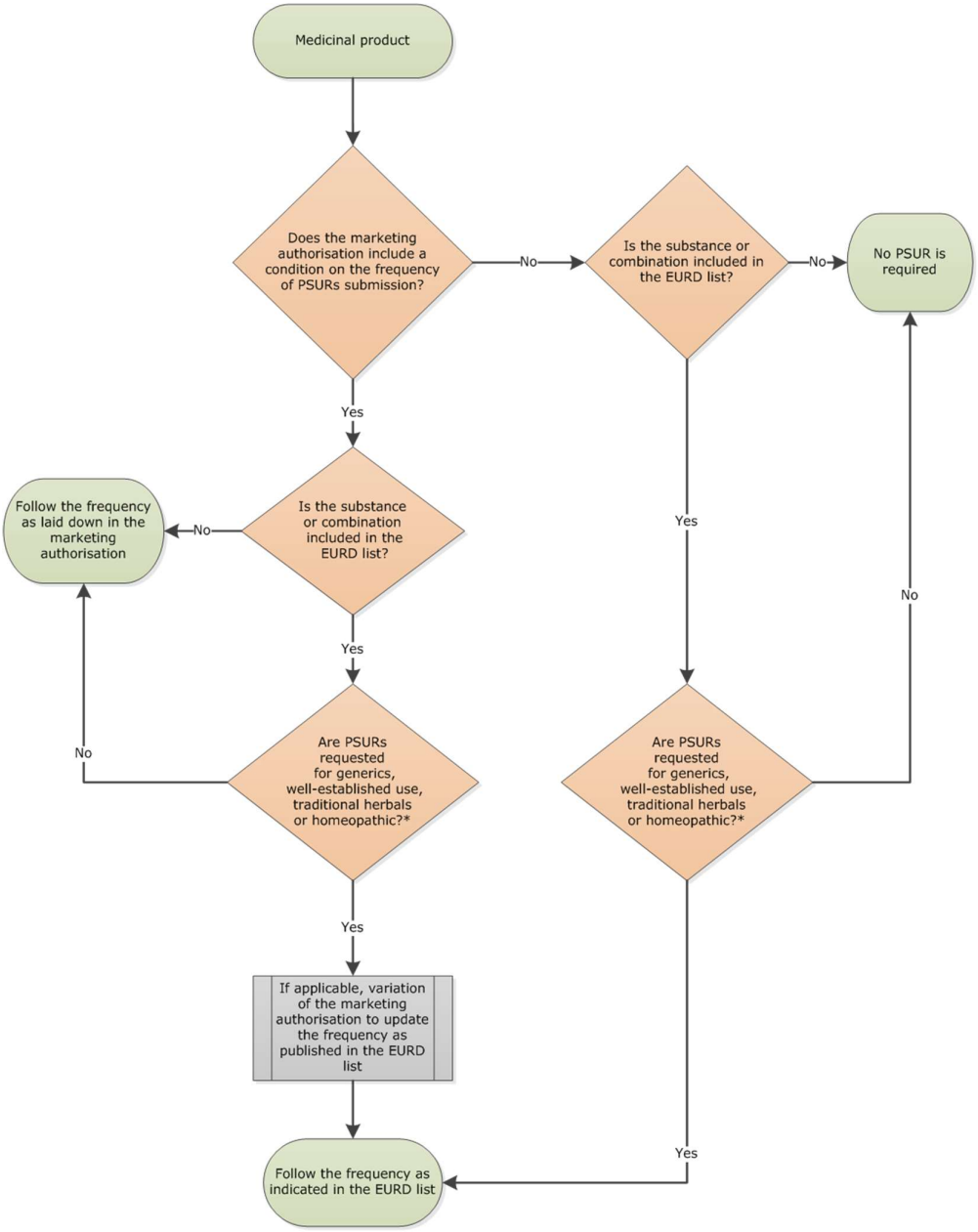
The harmonised frequency for the submission of the reports and the EU reference dates are determined by the CHMP and/or CMDh after consultation of the PRAC.

The application of the list of EU reference dates for the submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products does not undermine the right of a competent authority in a Member State to request the submission of PSURs at any time under the provision laid down in [DIR Art 107c(2) second subparagraph].

For products where PSURs are no longer required to be submitted routinely, it is expected that marketing authorisation holders will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the risk-benefit balance or the product information (See Module VI and Module IX).

Figure VII.4. presents the various potential scenarios as regard the submission of a PSUR for generic, well-established use, traditional herbal and homeopathic medicinal products:

Figure VII.4. Conditions for PSURs submission for generic, well-established use, traditional herbal and homeopathic medicinal products.



* Whether marketing authorisation holders for generics, well-established use, traditional herbal and homeopathic medicinal products are requested to submit PSURs following a request of a competent authority in a Member State due to concerns relating to pharmacovigilance data or lack of PSUR submission.

VII.C.3.3.3. Submission of PSURs for fixed dose combination products

Unless otherwise specified in the list of EU reference dates and frequency of submission, if the substance that is the subject of the PSUR is also authorised as a component of a fixed combination medicinal product, the marketing authorisation holder shall either submit a separate PSUR for the combination of active substances authorised for the same marketing authorisation holder with cross- references to the single-substance PSUR(s), or provide the combination data within one of the single- substance PSURs [IR Art 34(7)].

VII.C.3.3.4. Submission of PSURs on demand of a competent authority in a Member State

Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a Member State [DIR Art 107c(2)]. To facilitate the EU assessment and avoid duplication of requests, the competent authorities in the Member States should normally make use of the list of EU reference dates to request the submission of PSURs, however in especial circumstances competent authorities in Member States can directly request the submission of a PSUR. When the timeline for submission has not been specified in the request, marketing authorisation holders should submit the PSUR within 90 calendar days of the data lock point.

VII.C.3.4. Criteria used for defining the frequency of submission of PSURs

When deviating from the PSUR submission schedule defined in DIR Art 107c(2)(b), the frequencies of submission of PSURs and the corresponding data lock points should be defined on a risk-based approach by the CHMP where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure or by the CMDh otherwise, after consultation with the PRAC.

The following prioritisation criteria should be taken into account when defining the frequency of submission for a given active substance or combination of active substances:

- information on risks or benefits that may have an impact on the public health;
- new product for which there is limited safety information available to date (includes pre- and post- authorisation experiences);
- significant changes to the product (e.g. new indication has been authorised, new pharmaceutical form or route of administration broadening the exposed patient population);
- vulnerable patient populations/poorly studied patient populations, missing information (e.g. children, pregnant women) while these populations are likely to be exposed in the post-authorisation setting;

- signal of/potential for misuse, medication error, risk of overdose or dependency;
- the size of the safety database and exposure to the medicinal product;
- medicinal products subjected to additional monitoring.

Any change in the criteria listed above for a given active substance or combination of active substances may lead to an amendment of the list of EU reference dates (e.g. increase of the frequency for PSUR submission).

VII.C.3.5. Maintenance of the list of EU reference dates

VII.C.3.5.1. General principles

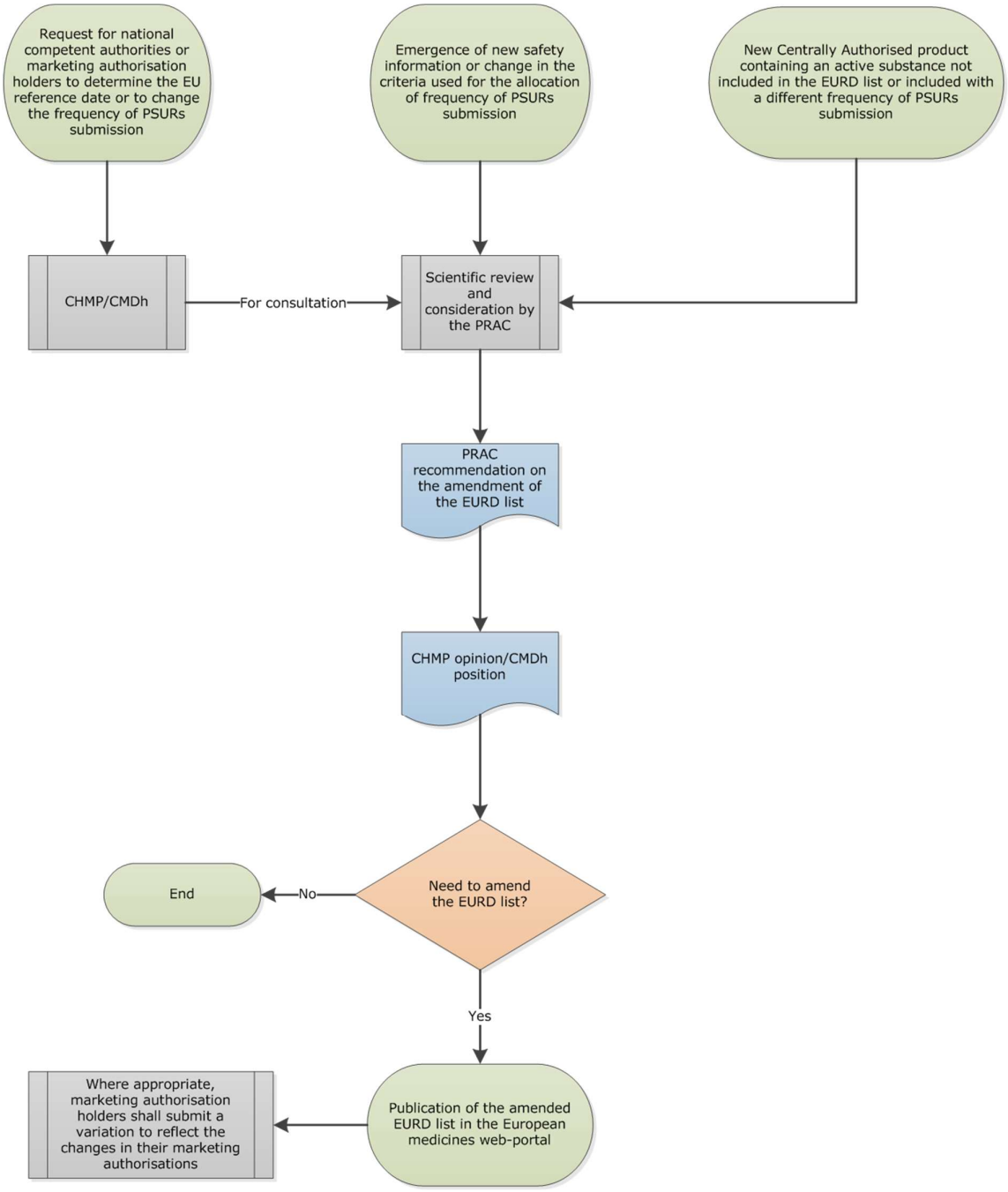
The maintenance of the list of EU reference dates should facilitate regulatory responsiveness to public health concerns identified within the EU and therefore the list will be subject to changes to reflect the decisions taken (e.g. by the Agency's committees following signal detection).

The information included in the list such as the active substances and combinations of active substances, the frequencies of submission of PSURs and data lock points may need to be updated when considered necessary by the CHMP or CMDh after consultation with the PRAC. Changes to the list may be applied on one of the following grounds:

- emergence of new information that might have an impact on the risk-benefit balance of the active substances or combinations of active substances, and potentially on public health;
- any change in the criteria used for the allocation of frequency for PSUR submission and defined under VII.C.3.4.;
- a request from the marketing authorisation holders as defined under DIR Art 107c(6);
- active substance newly authorised.

Figure VII.5. provides a general overview of the maintenance of the list of EU reference dates and frequency of submission of PSURs:

Figure VII.5. Maintenance of the list of EU reference dates and frequency of submission of PSURs



VII.C.3.5.2. Requests from marketing authorisation holders to amend the list of EU reference dates

Marketing authorisation holders shall be allowed to submit a request to the CHMP or the CMDh, as appropriate, to determine the Union reference dates or to change the frequency of submission of PSURs on one of the following grounds [DIR Art 107c(6)]:

- for reasons relating to public health;
- in order to avoid a duplication of the assessment;
- in order to achieve international harmonisation.

The request and its grounds should be considered by the PRAC and the CHMP if it concerns at least one marketing authorisation granted in accordance with the centralised procedure or the CMDh otherwise, which will either approve or deny the request.

The list will then be amended accordingly when appropriate and published on the European medicines web-portal (see section VII.C.3.6.).

For details about how to submit requests for amendments to the list, refer to the EU reference dates cover note and the related template published on the European medicines web-portal[21]

VII.C.3.6. Publication of the list

Upon its establishment and adoption by the CHMP and CMDh following PRAC consultation, the list of EU reference dates and frequency of submission of PSURs is published on the European medicines web- portal.

In case of amendments, the updated list should be published following its adoption by the CHMP or the CMDh. It is expected to be updated monthly.

VII.C.3.7. Amendment of the marketing authorisation according to the list of EU reference dates

Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six months after the date of the publication on the European medicines web-portal. Where appropriate, marketing authorisation holders shall submit the relevant variation in order to reflect the changes in their marketing authorisation [DIR 107c(6)], unless the marketing authorisation contains a direct cross reference to the list of EU references dates.

VII.C.4. Processes for PSUR Assessment in the EU network

The competent authorities in the Member States shall assess PSURs to determine whether there

are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of the medicinal product [DIR Art 107d].

For purely nationally authorised medicinal products authorised in one Member State, the assessment of PSURs is conducted by the competent authority in the Member State where the product is authorised (see VII.C.4.1.).

For medicinal products authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holders and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from the PRAC in accordance with the procedure described in VII.C.4.2.1. and VII.C.4.2.2..

Further to assessment of the PSUR and opinion from the CHMP or position from the CMDh, as applicable, following the recommendation from the PRAC, the competent authorities in Member States, or the European Commission for centrally authorised products, shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s), in accordance with outcome of the assessment [DIR Art 107g(2)] [REG Art 28(4) and (5)] (see VII.C.4.2.3. and VII.C.4.2.4.).

The outcome of the PSUR assessment results in a legally binding decision or position in case of any action to vary, suspend, revoke the marketing authorisations of the medicinal products containing the concerned active substance or combination of active substances, on the basis of the position of the CMDh or the opinion of the CHMP following the recommendations from the PRAC. Furthermore, marketing authorisation holders are reminded of their obligation to keep their marketing authorisation up to date in accordance with REG Art 16(3) and DIR Art 23(3). The recommendations are therefore implemented in a harmonised and timely manner for all products within the scope of the procedure across the EU.

Amendments to the SmPC, package leaflet and labelling as a result of the PSUR assessment should be implemented without subsequent variation submission for centrally authorised products and through the appropriate variation for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

When the proposals for the product information include new adverse reactions in section 4.8 ("Undesirable effects") of the SmPC, or modifications in the description, frequency and severity of the existing reactions, marketing authorisation holders should provide in the relevant sections of the PSUR appropriate information to allow the adequate description and classification of the frequency of the adverse reactions. If other sections of the SmPC (e.g. SmPC section 4.4 "Special warnings and precautions for use") are considered to be updated, clear proposals should be provided for the competent authorities in the Member States to consider during the PSUR

assessment[22]. The proposals should be included in the PSUR regional appendix (VII.C.5.).

Harmonisation of the entire product information in all the Member States where the product is authorised is not one of the objectives of the PSUR assessment procedure. Instead, the outcome of the assessment should incorporate the new safety warnings and key risk minimisation recommendations, arising from the assessment of the data in the PSUR, to be included in the relevant sections of the product information.

VII.C.4.1. PSURs for purely nationally authorised medicinal products

It is the responsibility of the competent authority in the Member State where the product is authorised to evaluate the PSURs for these medicinal products and the assessment is conducted in accordance with the national legislation.

Listings of individual cases may be requested in the context of the PSUR assessment procedure for adverse reactions of special interest and should be provided by the marketing authorisation holder within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual case safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

Following the assessment of PSURs, the competent authority in the Member State should consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary. They should vary, suspend or revoke the marketing authorisation when applicable according to the appropriate procedure at national level.

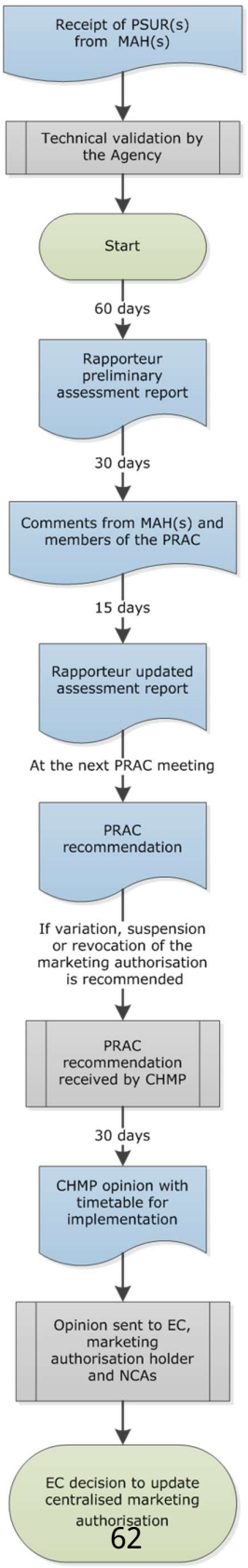
The assessment report and conclusions of the competent authority in the Member State should be provided to the marketing authorisation holder.

VII.C.4.2. Medicinal products authorised in more than one Member State

VII.C.4.2.1. Assessment of PSURs for a single centrally authorised medicinal product

This section describes the assessment of PSURs where only one centrally authorised medicinal product is involved according to the procedure set up in Article 28 of Regulation (EC) No 726/2004 (see figure VII.6.).

Figure VII.6. PSUR assessment procedure for a single centrally authorised medicinal product



The assessment of PSURs for a single centrally authorised medicinal product is coordinated by the Agency and shall be conducted by a Rapporteur appointed by the PRAC [REG Art 28(3)] (hereinafter referred to as "PRAC Rapporteur").

Upon receipt, the Agency should perform a technical validation of the report to ensure that the PSUR application is in a suitable format.

Listings of individual cases from EudraVigilance database may be retrieved to support the PSUR assessment.

Further to the above verifications, the procedure starts in accordance with the official starting dates published on the Agency's website. The detailed procedural timetables are published as a generic calendar on the Agency's website.

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur through the Agency for adverse reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual cases safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

During the drafting of the assessment report, the PRAC Rapporteur shall closely collaborate with the CHMP Rapporteur [REG Art 28(3)].

The PRAC Rapporteur shall prepare an assessment report and send it to the Agency and to the members of the PRAC [REG Art 28(3)] within 60 days of the start of the procedure.

The Agency shall send the PRAC Rapporteur's preliminary assessment report to the marketing authorisation holder [REG Art 28(3)].

By Day 90, the marketing authorisation holder and members of the PRAC may send comments on the PRAC Rapporteur's preliminary assessment report to the Agency and the PRAC Rapporteur. Those comments should also include responses to outstanding issues or questions raised by the PRAC Rapporteur in the preliminary assessment report and which can be addressed within the timeframe of the comments phase.

Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG Art 28(3)] within 15 days (i.e. by Day 105). The updated assessment report is made available to the members of the PRAC and should be forwarded to the marketing authorisation

holder by the Agency

An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The PRAC shall adopt the updated assessment report with or without further changes at its next meeting [REG Art 28(3)], together with a recommendation on the maintenance of the marketing authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC recommendation may also highlight the need to conduct a post-authorisation safety study, request an update of the RMP, review of safety issues and/or close monitoring of events of interest.

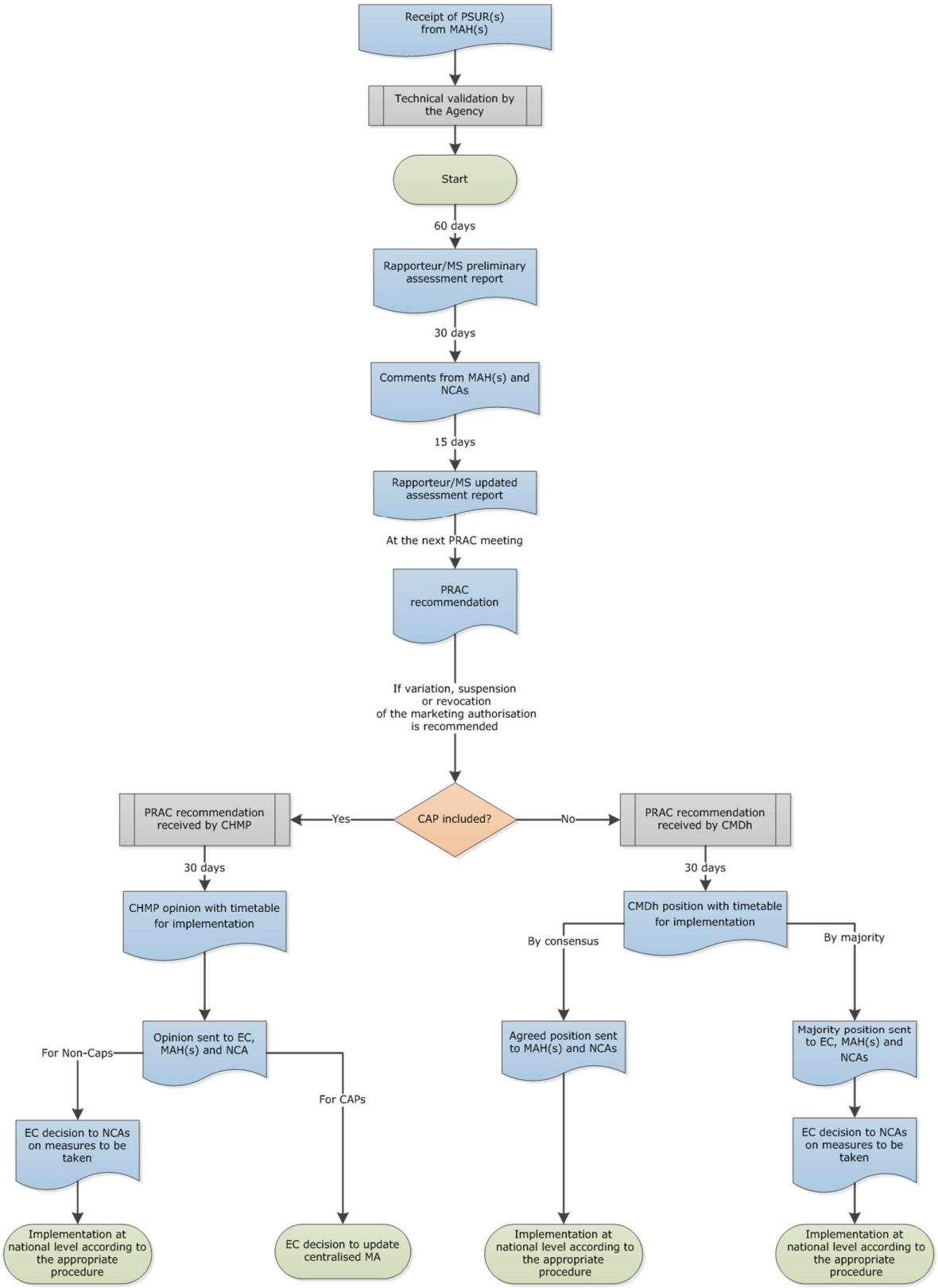
Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC [REG Art 28(3)]. The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder [REG Art 28(3)].

Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the assessment report and PRAC recommendation are sent to the CHMP for adoption of an opinion for the centrally authorised product concerned as described in VII.C.4.2.3..

VII.C.4.2.2. Assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance (EU single assessment)

This section describes the assessment of PSURs for medicinal products subject to different marketing authorisations, authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates. This could include a mixture of centrally authorised products, products authorised through the mutual recognition, decentralised and national procedures. [DIR Art 107e to 107g] (so-called PSUR “EU single assessment” procedure).

Figure VII.7. PSUR assessment procedure for "EU single assessment"



The assessment of PSURs for medicinal products, also called "EU single assessment", shall be conducted by [DIR Art 107e(1)]:

- a "Member State" appointed by the CMDh where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure;
- a "Rapporteur" appointed by the PRAC, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure (hereinafter referred to as "PRAC Rapporteur").

The PSUR EU single assessment procedure is coordinated by the Agency. Upon receipt, the Agency should perform a technical validation of the reports to ensure that the PSURs applications are in a suitable format.

Upon establishment of the list of all medicinal products for human use authorised in the EU referred to in REG Art 57, the Agency should ensure that all marketing authorisation holder(s) of the given substance have submitted PSUR(s), as required. In the event where a PSUR has not been submitted, the Agency should contact the concerned marketing authorisation holder(s). However, this will not preclude the start of the single assessment procedure for other PSUR(s) of the same active substance.

Listings of individual cases from EudraVigilance database may be retrieved to support the PSURs assessment.

Further to the above verifications, the procedure starts in accordance with the official starting dates published on the Agency's website. The detailed procedural timetables are published as a generic calendar on the Agency's website.

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

Further to the start of procedure, the PRAC Rapporteur or Member State conducts the single assessment of all PSURs submitted for the given active substance.

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur or Member State through the Agency for adverse drug reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual cases safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

The PRAC Rapporteur or Member State shall prepare an assessment report and send it to the

Agency and to the Member States concerned [DIR Art 107e(2)] within 60 days of the start of the procedure. This preliminary assessment report should be circulated to the members of the PRAC.

The Agency shall send the PRAC Rapporteur's/Member State preliminary assessment report to the concerned marketing authorisation holder(s) [DIR Art 107e(2)]. This assessment report should be circulated amongst all the marketing authorisation holders whose medicinal product(s) are part of the EU single assessment.

By Day 90, the marketing authorisation holder(s), Member States and members of the PRAC as applicable may send comments on the PRAC Rapporteur's/Member State's preliminary assessment report to the Agency and the PRAC Rapporteur/Member State, as applicable. Those comments should also include responses to outstanding issues or questions raised by the PRAC Rapporteur/Member State in the preliminary assessment report and which can be addressed within the timeframe of the comments phase.

Following receipt of comments, the PRAC Rapporteur/Member State shall prepare an updated assessment report [DIR Art 107e (3)] within 15 days (i.e. by Day 105). The updated assessment report is forwarded to the members of the PRAC and should be circulated by the Agency amongst all the marketing authorisation holders whose medicinal product(s) are part of the EU single assessment.

An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The PRAC shall adopt the updated assessment report with or without further changes at its next meeting [DIR Art 107e(3)], together with a recommendation on maintenance of the marketing authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC recommendation may also highlight the need to conduct a post-authorisation safety study (see Module VIII), request an update of the RMP (see Module V), review of safety issue and/or close monitoring of events of interest.

Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC [DIR Art 107e(3)].

The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder(s) [DIR Art 107e(3)].

Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the assessment report and PRAC recommendation are sent to:

- the CHMP where at least one centrally authorised product is included in the single

assessment, for adoption of an opinion as described in VII.C.4.2.3.;

- the CMDh where no centrally authorised product is included in the single assessment, for agreement of a position as described in VII.C.4.2.4..

VII.C.4.2.3. Single assessment including at least one centrally authorised product leading to a CHMP opinion

The CHMP acknowledges receipt of the PRAC recommendation and assessment report, in case of any regulatory action, at their next meeting following the PRAC adoption. Within 30 days from receipt, the CHMP shall consider the PRAC assessment report and recommendation and adopt an opinion on the maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned [DIR 107g(3)].

An oral explanation to the CHMP can be held at the request of the CHMP or the marketing authorisation holder(s) only in case of differences with the PRAC recommendation where CHMP considers the possibility of adopting an opinion on the suspension or revocation of the marketing authorisation(s), a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The opinion will contain the following:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable [DIR Art 107g(3)];
- in the case of a CHMP opinion to vary the marketing authorisation(s):

– the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation;

– for centrally authorised products, revised product information and if applicable, conditions imposed to the marketing authorisation holder and where appropriate, the conditions or restrictions imposed to the Member States for the safe and effective used of the medicinal product, in accordance with the provision provided in DIR Art 127a;

– for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures, an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information as applicable.

- in the case of a CHMP opinion to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;

- in the case of a CHMP opinion to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- divergent positions of CHMP members, where applicable.

Further to adoption, the Agency should send the CHMP opinion together with its annexes and appendices to the European Commission, marketing authorisation holder(s) and competent authorities in Member States.

The final assessment conclusions and recommendations are published in the European medicines web- portal (VII.C.7.).

a. Post CHMP opinion - Centrally authorised products

Where the CHMP opinion states that the terms of the marketing authorisation(s) needs to be varied, the marketing authorisation holder(s) of centrally authorised products should provide the translations of the product information and the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation, in all EU official languages, in accordance with the translation timetable adopted by the CHMP.

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt a decision addressed to marketing authorisation holders to vary, suspend or revoke the marketing authorisation(s) of centrally authorised product(s) [DIR Art 107g(4b)].

Further to adoption, the European Commission should notify the decisions amending the terms of the marketing authorisation of centrally authorised products to the marketing authorisation holder(s).

b. Post CHMP opinion - Nationally authorised products, including those authorised through the mutual recognition and decentralised procedures

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisations is necessary, the European Commission shall adopt a decision addressed to the competent authorities in Member States concerning the measures to be taken [DIR Art 107g(a)] in respect of nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

Further to the receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s) within 30 days [DIR Art 107g(4)].

VII.C.4.2.4. Single assessment not including centrally authorised product leading to a CMDh position

The CMDh acknowledges receipt of the PRAC recommendation and assessment report, in case of any regulatory action, at their next meeting following the PRAC adoption.

Within 30 days from receipt, the CMDh shall consider the PRAC assessment report and recommendation and reach a position on the maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned [DIR Art 107g(1)].

An oral explanation to the CMDh can be held at the request of the CMDh or the marketing authorisation holder(s), only in case of differences with the PRAC recommendation where the CMDh considers the possibility to reach a position on the suspension or revocation of the marketing authorisation(s), a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The position will contain the following:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable [DIR Art 107g(2)];
- in the case of a CMDh position to vary the marketing authorisation(s), the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation and an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information, as applicable;
- in the case of a CMDh position to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;
- in the case of a CMDh position to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- divergent position(s) for the CMDh members, where applicable.

The final assessment conclusions and recommendations shall be published by the Agency in the European medicines web-portal [DIR Art 107l] (VII.C.7.).

<u>If the CMDh position is reached by consensus:</u>

The position agreed including the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting where agreed.

The chairman shall send the agreed CMDh position [DIR Art 107g(2)] and its appendices to the

marketing authorisation holder(s) and competent authorities in Member States.

Further to receipt of the CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the competent authorities in Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation(s) concerned in accordance with the timetable for implementation determined in the agreed position [DIR Art 107g(2)].

In case the position of the CMDh agreed that variation to the terms of marketing authorisation is required, the marketing authorisation holder(s) shall submit the relevant variation to that effect within the timetable for implementation [DIR Art 107g(2)] as appended to the agreed position.

If the CMDh position is reached by majority vote:
The majority position on the action to be taken is recorded by the chairman in the minutes of the CMDh meeting where agreed.

The majority position of the CMDh together with its annexes and its appendices, including translations in all EU official languages where applicable, shall be forwarded to the European Commission [DIR Art 107g(2)]. The position of the CMDh should also be forwarded to the competent authorities in Member States.

Further to receipt of a CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt decision(s) [DIR Art 107g(2)] addressed to the competent authorities in Member States in order for them to vary, suspend or revoke the marketing authorisation(s) of nationally authorised product(s) which is addressed to marketing authorisation holders.

Further to receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to maintain, vary, suspend or revoke the marketing authorisation(s) within 30 days [DIR Art 107g(2)].

VII.C.4.3. Relationship between PSUR and risk management plan

The general relationship between the risk management plan (RMP) and the PSUR is described in Module V, while an overview of the common RMP/PSUR modules is provided in VII.C.4.3.1..

During the preparation of a PSUR, the marketing authorisation holder should consider whether any identified or potential risks discussed within the PSUR is important and requires an update of the RMP. In these circumstances, updated revised RMP including the new important safety concern should be submitted with the PSUR and assessed in parallel, following the timetable for the assessment of PSUR as described above.

If important safety concerns are identified by the national competent authorities in the Member

States during the assessment of a PSUR and no updated RMP or no RMP has been submitted, recommendations should be made to submit an update or a new RMP within a defined timeline.

VII.C.4.3.1. PSUR and risk management plan – common modules

The proposed modular formats for the PSUR and the RMP aim to address duplication and facilitate flexibility by enabling common PSUR/RMP sections to be utilised interchangeably across both reports. Common sections with the above mentioned reports are identified in Table VII.1.:

Table VII.1. Common sections between PSUR and RMP

PSUR section	RMP section
Section 3 – "Actions taken in the reporting interval for safety reasons"	Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"
Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"	Part II, module SV – "Post-authorisation experience", section "Non-study post- authorisation exposure"
Sub-section 16.1 – "Summary of safety concerns"	Part II, module SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)
Sub-section 16.4 – "Characterisation of risks"	Part II, Module SVII – "Identified and potential

PSUR section	RMP section
	risks”
Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”	Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”

VII.C.5. EU-specific requirements for periodic safety update reports

The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR detailed in VII.B.5. shall be based on all available data, including data from clinical trials in unauthorised indications and populations according to the provisions of DIR Art 107b and IR Art 34(1).

The EU-specific requirements should be included in the PSUR EU regional appendix.

VII.C.5.1. PSUR EU regional appendix, sub-section “Proposed product information”

The assessment of the need for amendments to the product information is incorporated within the PSUR assessment procedure in the EU. The regulatory opinion/position should include recommendations for updates to product information where needed. Marketing authorisation holders should provide the necessary supportive documentation and references within the PSUR or in this appendix to facilitate this.

Within the PSUR, the marketing authorisation holder is required to consider the impact of the data and evaluations presented within the report, on the marketing authorisation. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved SmPC(s) for the product(s) for which the PSUR is submitted [IR Art 34 (5)].

In this sub-section, the marketing authorisation holder should provide the proposals for product information (SmPC and package leaflet) based on the above mentioned evaluation. These should be based on all EU authorised indications.

A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed product information should also be submitted to Module 1.3.1 of the Electronic Common Technical Document (eCTD).

All the SmPCs and packages leaflets covered by the PSUR and in effect at the data lock point,

should be reviewed to ensure that they reflect the appropriate information according to the cumulative data included and analysed in the PSUR.

Amendments to the product information should not be postponed or delayed until the PSUR submission and amendments not related to the information presented in the PSUR, should not be proposed within the PSUR procedure. It is the obligation of the marketing authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a marketing authorisation.

A brief description of ongoing procedures (e.g. variations) to update the product information should be provided in this section.

VII.C.5.2. PSUR EU regional appendix, sub-section "Proposed additional pharmacovigilance and risk minimisation activities"

Considering the provision established in IR Art 34 (5), this sub-section should include proposals for additional pharmacovigilance and additional risk minimisation activities based on the conclusions and actions of the PSUR, including a statement of the intention to submit a RMP or an updated RMP when applicable.

VII.C.5.3. PSUR EU regional appendix, sub-section "Summary of ongoing safety concerns"

In order to support the information provided in the PSUR section 16.1 "Summary of safety concerns" (see VII.B.5.16.1.), Table 1.10 (according to the current RMP template) "Summary – Ongoing safety concerns" should be included in this PSUR sub-section. This table should be extracted from the version of RMP available at the beginning of the PSUR reporting interval (see Module V).

VII.C.5.4. PSUR EU regional appendix, sub-section "Reporting of results from post-authorisation safety studies"

Findings from both interventional and non-interventional (for further guidance see Module VIII) post- authorisation safety studies (PASS) should be reported in the PSUR. While the marketing authorisation holder should inform competent authorities in Member States and the Agency as applicable about any new information that may impact on the risk-benefit balance immediately, the PSUR should provide comprehensive information on the findings of all PASS, both interventional and non-interventional, in PSUR sections 7 and 8 respectively.

Final study reports for studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed during the reporting interval should also be included as an annex to the PSUR. For such studies discontinued during the reporting interval, the reasons for stopping the study should also be explained.

If an important safety concern has been identified in the course of a study, regardless of whether it has been detected through pre-specified methods and whether the study is considered a PASS, the marketing authorisation holder and specifically the qualified person responsible for pharmacovigilance (QPPV) will have informed the relevant competent authorities in Member States immediately.

PSURs should not be used as the initial communication method either for the submission of final study reports to the competent authorities in Member States or for the notification of any new

information that might influence the evaluation of the risk-benefit balance.

VII.C.5.5. PSUR EU regional appendix, sub-section "Effectiveness of risk minimisation"

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised. In accordance with section VII.B.5.16.5., evaluation of broad global experience should be reflected in the body of the report, when provides insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest.

This sub-section should additionally provide an evaluation of the effectiveness of routine and/or additional risk minimisation activities specifically relevant to an EU context. This should take account of regulatory imposed obligations for implementation of risk minimisation measures in addition to the overall requirement for monitoring of safety and benefit-risk. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities in the EU should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, then alternative activities need to be put in place. In certain cases, it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks. More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in Module
XVI. As a principle, the marketing authorisation holder should distinguish in their evaluation between implementation success and attainment of the intended outcome.

VII.C.6. Quality systems and record management systems for PSURs in the EU network

VII.C.6.1. Quality systems and record management systems at the level of the marketing authorisation holder

Specific quality system procedures and processes shall be in place in order to ensure the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal [IR Art 11(1)(f)].

It is the responsibility of the marketing authorisation holder to check regularly the list of EU reference dates and frequency of submission published in the European medicines web-portal to ensure compliance with the PSUR reporting requirements for their medicinal products (see VII.C.3.).

Systems should be in place to schedule the production of PSURs according to:

- the list of EU reference dates and frequency of PSURs submission; or
- the conditions laid down in the marketing authorisation; or
- the standard PSUR submission schedule established according to DIR Art 107c(2) for products authorised before 2 July 2012 (for centrally authorised products) and 21 July 2012 (for nationally authorised products) as applicable (without any conditions in their marketing authorisation or not included in the list of EU references dates and frequency of submission or not affected by the derogation established in [DIR Art 107b(3)]); or
- ad hoc requests for PSURs by a competent authority in a Member State or the Agency.

For those medicinal products where the submission of an RMP is not required, the marketing authorisation holder should maintain on file a specification of important identified risks, important potential risks and missing information in order to support the preparation of the PSURs.

The marketing authorisation holder should have procedures in place to follow the requirements established by the Agency for the submission of PSURs.

The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system [DIR Art 104(e)] and therefore should ensure that the pharmacovigilance system in place enables the compliance with the requirements established for the production and submission of PSURs. In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV in relation to PSURs should include:

- ensuring the necessary quality, including the correctness and completeness, of the data submitted in the PSURs;
- ensuring full response according to the timelines and within the procedure agreed (e.g. next PSUR) to any request from the competent authorities in Member States and the Agency related to PSURs;
- awareness of the PSUR and assessment report conclusions, PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions in order to ensure that appropriate action takes place.

The record retention times for product-related documents in Module I also apply to PSURs and

source documents related to the creation of PSURs, including documents related to actions taken for safety reasons, clinical trials and post-authorisation studies, relevant benefit information and documents utilised for the calculation of patient exposure.

VII.C.6.2. Quality systems and record management systems at the level of the European Medicines Agency

The application of the Agency's quality system (see Module I) should support compliance by the Agency when fulfilling its tasks and responsibilities for the management of PSUR procedures and EU single assessments.

The Agency should have in place a process to technically validate the completeness of PSUR submissions.

Line listings and summary tabulations from the EudraVigilance database utilised to support the PSUR assessment should be created using reports by means of the EudraVigilance data analysis system.

Effective communication and circulation of PSURs and related documents is crucial for the successful completeness of the procedure; therefore processes have to be in place for the circulation of documents between the Agency, marketing authorisation holders, the Commission and the competent authorities in Member States. Where applicable, the procedures should establish the necessity for quality checks with the aim to remove any information of a personal or commercially confidential nature.

Written procedures should reflect the different steps to follow for the maintenance of the list of EU references dates and frequency of submission of PSURs published by the Agency in the European medicines web-portal (see VII.C.3.).

Prior to the publication of summaries of PSUR assessment reports in the European medicines web- portal (see VII.C.7.) the appropriate personnel at the Agency should adhere to the procedures established for web publication of documents produced by the Agency or competent authorities in the Member States.

All records related to PSURs created by the Agency's staff members, experts or consultants are the property of the Agency and all PSURs and related documents received are in the custody of the Agency. Both types of PSURs records (created or received by the Agency) are subject to the Agency's overall control via the PSUR repository set up according to the provisions laid down in REG Art 25a.

The Agency's policy on records management (EMEA/590678/2007)[23], provides the basis for a consistent, sustainable and efficient records management program and it has been developed in

accordance with the commonly recognised international standard for records management, "ISO 15489-1:2001 Information and documentation – Records management[24]". According to the records classification stated by the Agency's policy, PSURs would be considered business, legal, evidential and research/historical value records.

The record retention times for product-related documents in Module I also apply to PSUR- system related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs, assessment reports, the data retrieved from the EudraVigilance database or other data used to support the PSUR assessment).

VII.C.6.3. Quality systems and record management systems at the level of the competent authorities in Member States

Each competent authority in the Member States shall have in place a pharmacovigilance system [DIR Art 101] for the surveillance of medicinal products and for receipt and evaluation of all pharmacovigilance data including PSURs. For the purpose of operating its tasks relating to PSURs in addition to the pharmacovigilance system the national competent authorities in Member States should implement a quality system (see Module I).

Competent authorities in the Member States should monitor marketing authorisation holders for compliance with regulatory obligations for PSURs. Additionally, competent authorities should exchange information in cases of non-compliance and take appropriate regulatory actions as required.

No PSUR assessment at EU level is foreseen for purely nationally authorised products authorised in only one Member State; therefore the national competent authority in the Member State where the medicinal product is authorised should have procedures in place for the assessment of PSURs related to those medicinal products.

The procedures established by the national competent authorities in Member States for the performance of the EU single assessment of PSURs, should be in line with the procedures established by the Agency for the coordination of PSUR assessment in the EU regulatory network (see VII.C.4.). These procedures should establish effective communication across the EU regulatory network and the actions to be taken regarding the variation, suspension or revocation of the marketing authorisation following the PRAC recommendations, CHMP opinion, CMDh position and European Commission decision as applicable.

The procedures established by the Agency for the use of the PSUR repository to support the single assessment, should be followed by the national competent authorities in Member States.

Where tasks related to PSUR procedures are delegated to third parties, the national competent

authorities in Member States should ensure that they are subject to a quality system in compliance with the obligations provided by the European legislation.

The record retention times for product-related documents in Module I also apply to PSUR- system related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs, assessment reports, the data retrieved from the EudraVigilance database or other data used to support the PSUR assessment).

VII.C.7. Transparency

VII.C.7.1. Publication of PSUR-related documents on the European medicines and national medicines web-portals

The following documents shall be made publicly available by means of the European medicines web- portal [DIR Art 107l, REG Art 26(g)]:

- list of EU reference dates and frequency of submission of PSURs (see VII C.3.);
- final assessment conclusions of the adopted assessment reports;
- PRAC recommendations including relevant annexes;
- CMDh position including relevant annexes and where applicable, detailed explanation on scientific grounds for any differences with the PRAC recommendations;
- CHMP opinion including relevant annexes and where applicable, detailed explanation on scientific grounds for any differences with the PRAC recommendations;
- European Commission decision.

The version and date of publication are reflected in each document as they define the issue of the PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions at a certain point of time.

Links between the European medicines web-portal and the National medicines web-portals should be made whenever possible and relevant.

Any personal or confidential data made public by the Agency or the competent authorities in Member States as referred to in paragraphs 2 and 3 of Article 106a of Directive 2001/83/EC shall be deleted unless considered necessary in terms of protection of the public health [DIR Art 106a(4)].

VII.C.8. Renewal of marketing authorisations

Marketing authorisations need to be renewed after 5 years on the basis of a re-evaluation of the risk- benefit balance in order to continue to be valid to place the product on the market. This renewal is irrespective of whether the marketing authorisation is suspended. Further details on the procedure and the documentation requirements can be found in the current versions of the "Guideline on Processing of Renewals in the Centralised Procedure" (EMEA/CHMP/2990/00) for Centralised products and the "CMDh Best Practice Guide on the processing of renewals in the MRP/DCP" (CMDh/004/2005) for other products.

No PSURs, addendum reports and summary bridging reports should be submitted within the renewal application. The clinical overview should include an addendum containing the relevant sections for the re-assessment of the risk-benefit balance of the medicinal product. These sections are identified in the above-mentioned guidelines for renewal. Marketing authorisation holders are advised to consider this GVP Module VII as guidance for the preparation of the addendum to the clinical overview.

Following the submission of a renewal application, the PRAC may be consulted for medicinal products authorised through the centralised procedure as regards safety issues. For nationally authorised products, including those authorised through the mutual recognition or decentralised procedure, the PRAC may also be consulted upon request by a competent authority in a Member State on the basis of safety concerns.

Conditional marketing authorisations should be renewed annually [REG Art 14(7)]. Further details on the procedure and the documentation to be submitted can be found in the "Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) no 726/2004" (EMEA/509951/2006).

VII.C.9. Transition and interim arrangements

VII.C.9.1. Submission and availability of documents before the Agency's repository is in place

The Agency shall, in collaboration with the competent authorities in Member States and the European Commission set up and maintain a repository for PSURs and the corresponding assessment reports so that they are fully and permanently accessible to European Commission, the competent authorities in Member States, the PRAC, the CHMP and the CMDh [REG Art 25a].

The repository shall undergo an independent audit before the functionalities are announced by the Agency's management board [REG Art 25a].

As established in the transitional provisions introduced in Directive 2010/84/EU Art 2(7), until the Agency can ensure the functionalities agreed for the repository, marketing authorisation holders under the obligation to submit PSURs irrespective of whether the medicinal product is authorised in one or more Member States and irrespective of whether the active substance or combination of active substances is on the EU reference date list shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised. For the substances or combination of active substances subject to the EU single assessment, and for which an EU reference date has been established, the PSURs should be also sent to the Agency.

The competent authorities in Member States requirements for the submission of PSURs during this transitional period are published in the Agency web-site[25].

From 12 months after the functionalities of the repository have been established and have been announced by the Agency, the marketing authorisation holders shall submit the PSURs electronically to the Agency regardless of the authorisation procedure of the medicinal product [DIR Art 107b(1)]. The competent authorities in Member States shall ensure that this obligation applies as required [DIR Art 2(7)].

Once the structured electronic format "ePSUR", based on content agreed in the ICH-E2C(R2), becomes available, marketing authorisation holders will have the possibility to submit PSURs and related documents automatically via an electronic gateway.

Until the repository is in place, the relevant documents should be circulated as follows:

- The preliminary assessment report created by the PRAC Rapporteur/Member State within 60 days of the start of the procedure should be circulated to the Agency and the members of the PRAC through a dedicated mailbox. The Agency should send the report to the concerned marketing authorisation holder(s);
- members of the PRAC should circulate their comments through a dedicated mailbox by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report;
- comments by the marketing authorisation holders(s) by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report, should be submitted to the Agency, PRAC Rapporteur and all members of the PRAC, according to the instructions for submission published by the Agency;
- updated PRAC Rapporteur/Member State assessment report created within 15 days (i.e. by Day 105) should be circulated to the Agency and members of the PRAC through a dedicated mailbox. The Agency should forward the updated PRAC Rapporteur/Member State assessment report to the marketing authorisation holders concerned.

Further to adoption, the Agency should send the CHMP opinion together with its annexes and appendices to the European Commission, marketing authorisation holder(s) and competent authorities in Member States, through secure email until the repository is in place.

VII.C.9.2. Quality systems and record management systems at the level of the competent authorities in Member States

Special considerations should be taken for the management of the PSURs submitted to the

concerned competent authorities in Member States until the Agency can ensure the functionalities agreed for the PSUR repository and 12 months after the establishment of the repository according to the transitional provisions.

VII.C.9.3. Publication of the EU list of union references dates and start of the EU- PSUR single assessment procedure

As stated in VII.C.3.6., the list of EU reference dates and frequency of submission should be published in the European medicines web-portal, nevertheless, the EU single assessment procedure for substances included only in nationally authorised products, detailed in VII.C.4.2.2., and VII.C.4.2.4. will be delayed until funds are available.

Question Bank

1. Explain the importance and purpose of PSUR
2. Write about various regulatory requirement of PSUR
3. Describe the process of PSUR preparation, submission and assessment.

References

1. A Handbook of Bioanalysis and Drug Metabolism by Gary Evans.
2. Clinical trial risk management by Martin Robinson & Simon Cook.
3. Clinical Trials: A Practical Guide to Design, Analysis & Reporting by Duolao Wang & Ameet Bakhai.
4. Data Monitoring committees in Clinical Trials Ebook by Susan S Ellenberg, Thomas R Flemming, David L Demets.
5. Drug Safety Evaluation by Shayne C Gad.
6. Guideline for Drug Regulatory Submissions by Sandy Weiberg.
7. Handbook of Bioequivalence testing by Sarfaraz K. Niazi.