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REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH E2E: Pharmacovigilance Planning (PvP)
Draft Version 4.1 dated on 11th November 2003

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1. Introduction

1.1 Objective

This guideline is intended to aid industry and regulators in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug.

The guideline describes a method for summarizing the identified risks of a drug, the potential for important unidentified risks, and the potentially at-risk populations and situations 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.

Although 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 background 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 essential 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 license is granted. This ICH guideline has been developed to encourage harmonization 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 and biotechnology-derived products, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process of a biotechnologically-derived product) and for established products that are to be introduced to new populations or in significant new indications.

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

- Pharmacovigilance Specification
- Pharmacovigilance Plan
- Annex – Pharmacovigilance Methods

The main focus of this guideline is on a Pharmacovigilance Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The guideline can be used to develop a stand-alone document for regions that prefer this approach or to provide guidance for sponsors who incorporate elements of the Pharmacovigilance Specification and Pharmacovigilance Plan into the Common Technical Document (CTD). 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 Pharmacovigilance Specification and Pharmacovigilance Plan can 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.

For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan.

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

This guideline is underpinned by the following principles:

- 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. Pharmacovigilance Specification

The Pharmacovigilance Specification is a summary of the identified risks of a drug, the potential for important unidentified risks, the populations potentially at-risk and situations that have not been adequately studied. This Pharmacovigilance Specification is intended to help industry and regulators identify any need for specific data collection in the post-approval period and also to facilitate the construction of the Pharmacovigilance Plan.

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 Pharmacovigilance Specification. Companies should support the Pharmacovigilance Specification with references to specific pages of the CTD or other relevant documents. The Pharmacovigilance Specification can be a stand-alone document, usually in conjunction with the Pharmacovigilance Plan, but elements can also be incorporated into the CTD for a new or modified product. 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 Pharmacovigilance Specification. The elements of the Pharmacovigilance Specification that are included are only a guide. The Pharmacovigilance 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 Pharmacovigilance 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 concerns that have not been resolved by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, genotoxicity, carcinogenicity etc.),
- General pharmacology (cardiovascular (including QT interval prolongation), nervous system, etc.),
- Effect of hepatic and renal dysfunction,
- Drug interactions, and
- 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 in medical practice.

For world-wide marketing experience, the following should be briefly discussed:

- The extent of the world-wide exposure,
- Any new or different safety issues identified, and
- 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 hepatic or renal disorders,
- Sub-populations with genetic polymorphisms, and
- Patients of different ethnic origins.

c. Adverse events (AEs) / Adverse drug reactions (ADRs)

This section should list the important identified and potential risks that require further characterization 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).

Safety issues that require further evaluation

More detailed information should be included on the most important identified 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, and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These 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 defined in this section. The evidence that led to the conclusion that there was a potential risk should be discussed. It is anticipated that for any important potential risk, there should be further evaluation to characterize 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 summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

e. Epidemiology of the indication(s) and important adverse events

The epidemiology of the indication(s) and important adverse events in the target population should be discussed. This discussion should include incidence, prevalence, and mortality, and should take into account whenever possible stratification by age, sex, and ethnic origin. Differences in the epidemiology in the different regions should be discussed, where this information is available.

f. Pharmacological class effects

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

2.2 Summary – Ongoing safety issues

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

- Important identified risks,
- Important potential risks, and
- Important missing information.

3. Pharmacovigilance Plan

3.1 Purpose

This section gives guidance on the structure of a Pharmacovigilance Plan. The Pharmacovigilance Plan should be based on the Pharmacovigilance 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 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 a new or modified product.

For products for which no special concerns have arisen, routine pharmacovigilance might be considered 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.

3.2 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 Pharmacovigilance Specification.

3.2.1 Summary of ongoing safety issues [see 2.2]

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

- Important identified risks,
- Important potential risks, and
- Important missing information.

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

3.2.2 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 organization and practices for conducting pharmacovigilance.

3.2.3 Safety action plan for specific issues/ important missing information

The plan for each important risk issue or important piece of missing information should be presented and justified according to the following structure:

- Risk issue or missing information,
- Objective of proposed action(s),
- Action(s) proposed,
- Rationale for proposed action(s),

- Oversight within the company for safety issue and proposed action(s), and
- 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).

3.2.4 Summary of actions to be completed, including milestones

An overall Pharmacovigilance Plan for the product bringing together the actions for all individual risk issues and missing information should be presented. Whereas section 3.2.3 suggests presenting an action plan by ongoing safety issue, for this section the pharmacovigilance plan for the product should be organized 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/characterization of the ADRs of concern or refutation of a particular concern, and/or
- the results of ongoing or proposed safety studies will be available.

These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment and license renewals).

3.3 Pharmacovigilance methods

The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid companies considering possible methods to address specific issues identified by the Pharmacovigilance Specification. 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 to choose 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.

3.3.1 Design and Conduct of Observational Studies

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non-interventional) studies, are important tools in pharmacovigilance. According to CIOMS Working Group V, "observational studies are sometimes referred to as non-experimental studies, in that the investigator observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice".

Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalized. It is desirable that pharmacoepidemiologists be consulted when developing the protocol. 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 should 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 analytic plan. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings.

Good epidemiological practice should be followed for observational studies (ref.1). It is recommended that the sponsor follow internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology (ref.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. In addition, in some ICH regions, interventional post-marketing safety studies should comply with the guidelines for GCP (ICH E6).

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

4. References

1) Chemical Manufacturers Association's Epidemiology Task Group. Guideline for good epidemiology practices for occupational environmental epidemiologic research. Journal of Occupational Medicine 1991; 33: 1221-1229.
2) International Society for Pharmacoepidemiology. Guidelines for Good Epidemiological Practices for Drug, Device and Vaccine Research in the United States. Pharmacoepidemiology and Drug Safety 1996; 5 (5): 333-338.

ANNEX - Pharmacovigilance Methods

1. Passive Surveillance

- Spontaneous reports

Spontaneous reports are those adverse drug events/reactions that are voluntarily reported either to pharmaceutical manufacturers, to national or regional pharmacovigilance centers, or to national regulatory authorities by healthcare professionals, other professionals or consumers.[1,2]

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 are not detected in earlier clinical trials or other pre-marketing studies. They can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised, though, 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.[3,4,5,6]

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 techniques for signal detection[7,8,9]. Data mining techniques have also been used to examine drug-drug interactions[10]. 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. Caution should be exercised if using this tool for evaluating the magnitude of risk or for comparing safety risks between 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 between different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing 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 [11,12]. Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on such reports for detailed and rapid follow-up.

2. Intensified 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[2]. Such methods included 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.

- Stimulated reporting in the early post-marketing phase

During the early post-marketing phase, drug manufacturers 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 drug manufacturers to notify healthcare professionals of new therapies and provide safety information early in use by the general population. This is still a form of spontaneous event reporting. Thus data obtained from stimulated reporting can not 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-organized 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. 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 the potential for 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, hemodialysis centers, 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[1,2,15,16]. Limitations of drug event monitoring 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 standardized 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 within the registry with another condition, or outside the registry.

  Exposure (drug) registries address populations exposed to medicinal products 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 standardized 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)[1,2].

- 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 utilized 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, which 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[1,2,17]. 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 metabolize 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[1]. 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 utilization study

Drug utilization 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[2]. 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 may include a lack of clinical outcome data or information of the indication for use of a product.

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