PV ICH E2E Guidelines

Module 9 Topic 7

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 guideline describes a method for summarizing 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

Definition

'Pharmacovigilance' is defined

"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems."

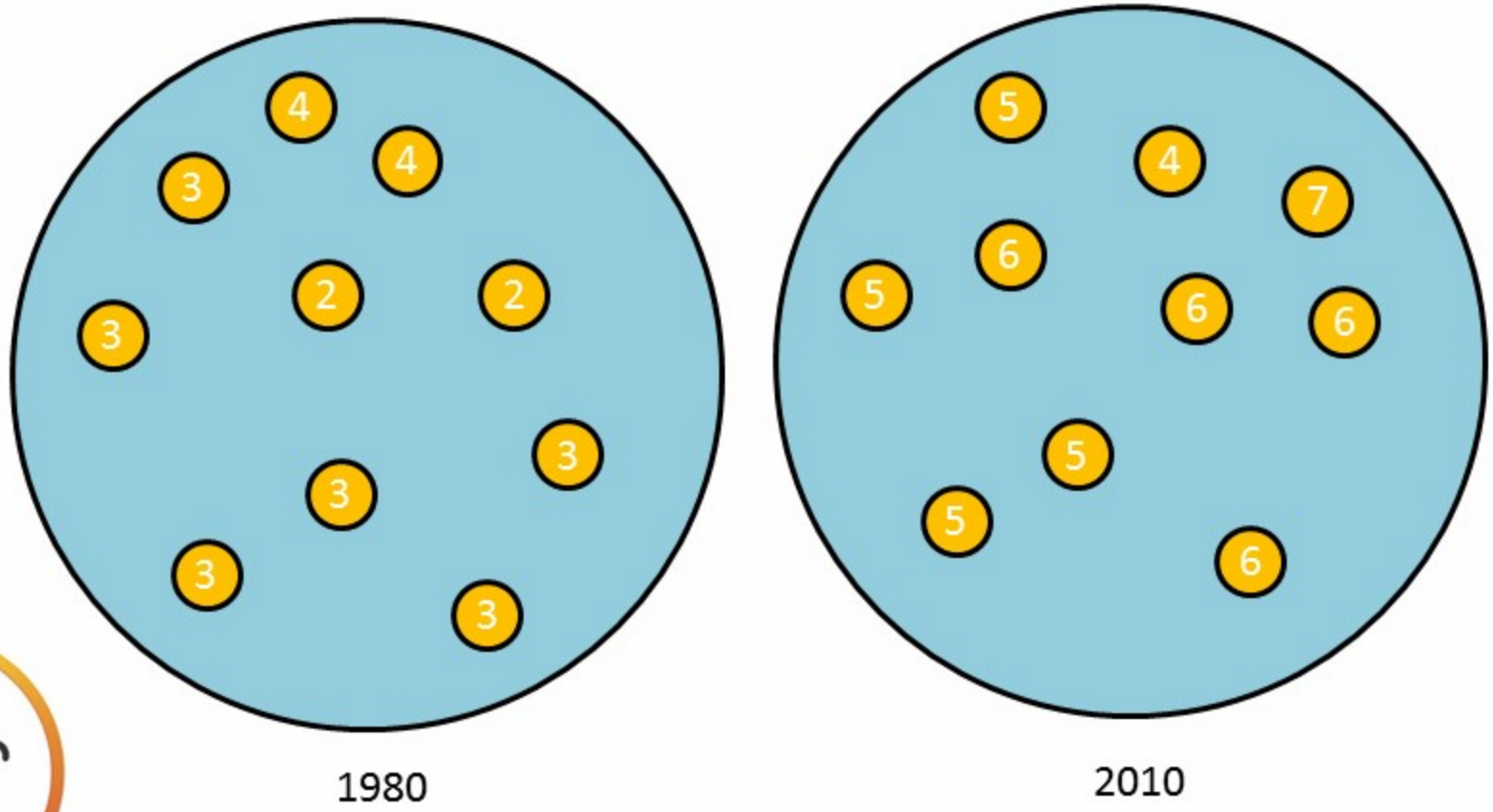
-WHO

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.

Example

New Drug with Benefit/Risk Ratio =4



1980

2010

Explanation

- A new Drug with a Benefit /Risk ratio of 4, was approvable in 1980, when most other drugs for the same indication in the market had a poorer B/R ratio
- In 2010 when most drugs in the market have a ratio more than 4, the new drug with a ratio of 4 may not be approvable

Post Marketing

- 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
- In the post marketing phase, other new products would be launched for the same indication, which might prove to be more beneficial leading to an erosion of the value of the title product. Continuous research will enable in bench marking the titled product against other products

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
- Also by curtailing the type of users to exclude those at high risk

Scope

- New Chemical Entities,
- Biotechnology-derived products,
- 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

ICH E2E

Safety Specification;

Pharmacovigilance Plan;

Pharmacovigilance Methods.

Pharmacovigilance

- Products yet to be marketed
  - Initiate plan well before making an NDA, dialogue with regulators
- Products already in the market
  - Collect safety information and set up a pharmacovigilance plan if one is not in place

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

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

Safety Specification (SS)

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

Sources of Information (SS)

- The Common Technical Document (CTD), especially the Overview of Safety, Benefits and Risks Conclusions, and the Summary of Clinical Safety sections, includes information relating to the safety of the product, and should be the basis of the safety issues identified in the Safety Specification

Elements of SS

- Non Clinical
- 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

Elements of SS (contd)

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

Elements of SS (contd)

- Possible risks in populations not studied

- 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.

Elements of SS (contd)

- Adverse Drug Effects
- Those observed in clinical studies
- Those not observed in clinical studies, but could be expected on the basis of class effects

Elements of SS (contd)

Drug Interactions

Drug-Drug Interactions

Drug Food Interactions

Drug environment interactions

Elements of SS (contd)

Epidemiology of the Indication

- Incidence, prevalence
- Gender
- Age groups at risk
- Racial or ethnic peculiarities

PV Plan

- Routine PV plan for products where no special risks have been identified

- Specific PV plan for those products where specific risk has been identified.

Routine PV Plan

- Systems and processes that ensure that information about all suspected adverse reactions that are reported 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

Important Safety Issues

- 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.

Examples of Actions

- Shake well before using
- Do not take on empty stomach

Study Milestone

Completion

- 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.

PV Methods

- Passive Surveillance
- Stimulated Reporting
- Active Surveillance
- Comparative Observational Studies
- Targeted Clinical Investigations
- Descriptive Studies.

Passive Surveillance

- Spontaneous Reports

- 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 organized data collection scheme

Advantages

- Come in only after marketing of the drug
- Have played a major role in identifying and quantitating risks
- Provide information on at risk groups, risk factors and clinical features of risks

Disadvantages

- Often incomplete
- Usually under reporting takes place
- May not be reliable when adverse effects of products are being compared.

Case Series

- A number of case reports on a single drug reporting similar adverse events are known as a case series.
- A case series often provides evidence of association between the drug and the adverse effect while helping in identifying the population at risk, and associated factors. It may be used for generating a hypothesis too!

Stimulated Reporting

- Reporting by health professionals who have been encouraged and facilitated to report adverse events
- Generally refer to a particular setting (hospital or an epidemic) for a limited period of time(generally in the early marketing phase)

Active Surveillance

- Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process

- This may be achieved by selecting sites or particular adverse events

Sentinel Sites

- Certain sites could be chosen to perform pharamcovigilance. These sites could be specialized centers handling a particular type of reaction (hemodialysis centers for nephrotoxic drugs)
- Weakness of this method is selection bias, small number of patients and high costs

Drug Event Monitoring

- A method of active pharmacovigilance surveillance, in which 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

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