Pharmacovigilance: Monitoring the safety of medicines

Introduction

Pharmacovigilance (PV) is the monitoring of medicine use for negative outcomes, or ‘adverse events’. A more formal definition is ‘the science and practice relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.’ The World Health Organisation (WHO) established its Programme for International Drug Monitoring in response to the thalidomide disaster revealed in 1961. This marked the beginning of international pharmacovigilance.

The company that holds the marketing authorisation for a medicine, the Marketing Authorisation Holder (MAH), has a legal obligation to continuously collect data and ensure pharmacovigilance. Data must be transmitted to the authorities within defined timelines, and any emerging concern about the benefit-risk balance must be brought to their attention immediately. If necessary, the authorities may request further investigations, including formal studies. Regulatory procedures exist for the processes of updating product information and implementing other safety measures.

Pharmacovigilance basics: Aims and scope

Pharmacovigilance activities aim to:

- improve patient care and safety in relation to the use of medicines and all medical interventions,
- improve public health and safety in relation to the use

of medicines,
- contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, **and**
- promote understanding, education, and clinical training in pharmacovigilance.

The scope of pharmacovigilance activities covers:

- Small molecule medicinal products, usually derived from chemical synthesis
- Herbal medicines and dietary supplements
- Traditional and complementary medicines
- Blood products
- Biologics (medicines derived from a biological source or living cells, such as antigens or vaccines)
- Medical devices
- Substandard medicines and counterfeit medicines

Benefit-risk balance

Medicines may affect the body in unintended, harmful ways. These effects, called side effects or adverse reactions, represent the risks of medicines (see section ‘Adverse events’ below). By the time a new medicine obtains a marketing authorisation, the medicine has been tested and the data have allowed the conclusion to be drawn that the benefits of the medicine outweigh its risks (pre-marketing status). However, once the medicine has obtained a marketing authorisation (post-marketing status), it will be used in normal healthcare settings for many patients who may differ from the study population (who were selected on defined criteria), for example by age or by having additional diseases. In addition, rare side effects might become evident only during extended periods of use as opposed to the limited time periods of clinical trials. It is therefore important to identify any new or changing risks of a medicine as quickly as possible, and to take measures to minimise risk and promote safe and effective

use.

Adverse events

An adverse event (AE) is any negative or harmful medical occurrence in a patient treated with a medicinal product, whether or not the AE is considered to be associated with that product. An AE does not necessarily have a causal relationship with the treatment. Some examples of AEs are:

- Suspected interactions with other medicines (medicine-medicine interactions),
- Drug abuse,
- Medication errors (such as taking too much of the medicine),
- Product technical complaints,
- Events resulting from overdose,
- Lack of expected medicine effect,
- Worsening of illness after the use of a product, **and**
- Birth defects and other events after use of the product during pregnancy.

A Serious Adverse Event (SAE) involves:

- Death,
- An immediately life-threatening event,
- Hospitalisation or extended hospitalisation,
- Significant or persistent disability,
- Birth defect or congenital anomaly, **or**
- Any important medical event that may jeopardise the patient or might require intervention(s) to prevent one of the outcomes listed above.

Periodic Safety Update Reports

(PSURs)

Periodic Safety Update Reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the benefit-risk balance of a medicinal product. PSURs must be submitted by an MAH at defined points of time during the post-authorisation phase. They present a comprehensive, concise, and critical analysis of the benefit-risk balance of a medicinal product, taking into account any new or emerging information in the context of the global cumulative information about the medicinal product. The European Medicines Agency (EMA) maintains a list of EU reference dates (EURDs) and frequency of submission of PSURs for active substances contained in medicinal products in the EU. The EMA carries out single assessments of related PSURs for medicinal products containing the same active substances or combinations of active substances.

Development Safety Update Reports (DSURs)

Development Safety Update Reports (DSURs) are documents intended to be a common standard for periodic reporting on medicinal products under development (including marketed medicines that are undergoing further study). Their main objective is to present a comprehensive, annual review and evaluation of pertinent study information collected during the reporting period, to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational medicinal products. It is also important to inform regulators and other interested parties (such as ethics committees) about the results of such analyses and to apprise them of actions proposed or being taken to address safety concerns.

Post-authorisation efficacy studies (PAES)

While the main focus of pharmacovigilance is the safety of the medicinal product, any new information received or new pharmacovigilance signals detected may have a potential impact on the overall product assessment and more particularly on its benefit-risk balance. According to the recitals of the new pharmacovigilance legislation, post-authorisation efficacy studies (PAESs) and post-authorisation safety studies (PASSs) may be aimed at collecting data to enable the assessment of efficacy or safety of medicinal products for human use in everyday medical practice.

PAESs may be required if, at the time of the initial marketing authorisation, concerns relating to aspects of the efficacy of the medicinal product are identified that can only be resolved after the medicinal product has been marketed. PAESs may also be required if the understanding of the disease or the clinical methodology indicates that previous efficacy evaluations might need to be significantly revised. PAESs are meant to provide the competent authorities and the MAH with the information required to either complement initial evidence or verify whether the marketing authorisation should be maintained as granted, varied, or even withdrawn on the basis of the new data resulting from the study.

Post-authorisation safety studies (PASS)

A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures. A PASS may be initiated, managed, or financed

voluntarily by an MAH or pursuant to an obligation imposed by a competent authority.

Public hearings

A public hearing is a forum to which the public is invited to express its views, guided by a pre-defined set of questions, on issues related to the safety of a particular medicinal product, medicinal substance, or therapeutic class, while also considering the therapeutic effects of these products.

Public hearings give the Pharmacovigilance Risk Assessment Committee (PRAC) – which is the committee at the EMA responsible for assessing and monitoring safety issues for human medicines – an opportunity to hear from the public and take their views into account in their opinion-making. This applies particularly where options for regulatory actions and risk management activities will need to be considered in a wider public-health context. Public hearings can add various elements to the debate.

The primary purpose of a public hearing is to hear views on the acceptability of the risks associated with the medicinal product/pharmaceutical ingredient/class of medicinal products concerned, particularly in relation to its therapeutic effects and any available therapeutic alternatives. Public hearings also aim to seek suggestions and recommendations on the feasibility and acceptability of risk management and minimisation activities.

Public hearings are open to all members of the public. The PRAC may proactively invite representatives of patients, consumers, healthcare professionals, or researchers with specific expertise in relation to the medicine(s) concerned. The MAHs also have the opportunity to present their view(s) to the participants of the public hearing.

Further Resources

- World Health Organization (2002). *The importance of pharmacovigilance: Safety monitoring of medicinal products.* Geneva: World Health Organization. Retrieved 12 July, 2021, from https://www.who.int/publications/i/item/10665-42493

Attachments

- Presentation: Introduction to pharmacovigilance: Monitoring the safety of medicines
  Size: 356,628 bytes, Format: .pptx
  An introduction to the scope, aims, and history of pharmacovigilance.

- Presentation: Aspects of Pharmacovigilance: Development Safety Update Report (DSURs)
  Size: 355,658 bytes, Format: .pptx
  Information on the definition, aims, and scope of Development Safety Update Reports (DSURs).

- Presentation: Aspects of Pharmacovigilance: Post-Authorisation Efficacy Studies (PAESs)
  Size: 360,920 bytes, Format: .pptx
  More information on the definition, aims, and scope of Post-Authorisation Efficacy Studies (PAESs).

- Presentation: Aspects of Pharmacovigilance: Post-Authorisation Safety Studies (PASSs)

Size: 354,087 bytes, Format: .pptx

More information on the definition, scope, and aims of Post-Authorisation Safety Studies (PASSs).

- Presentations: Aspects of Pharmacovigilance: Periodic Safety Update Reports (PSURs)

  Size: 355,384 bytes, Format: .pptx

  More information on the definition, scope, and aims of Periodic Safety Update Reports (PSURs).

- Presentation: Aspects of Pharmacovigilance: Public Hearings

  Size: 400,651 bytes, Format: .pptx

  Learn about the aims and decision-making processes behind public hearings, as well as how to attend and participate in them.

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