



Pharmacovigilance, international classification of diseases and adverse reaction reporting tools used in the United States of America and Europe

Abstract

Adverse Drug Reaction (ADR) identification is the most important goal during the post-marketing phase. ADR identification is needed for the surveillance of drug safety. The spontaneous reporting of ADR and using collected data related to every product is used for hypothesis generation and also for validation of new approaches. In the United States of America U.S, Food and Drug Administration (FDA) helps to study and find the adverse drug reaction data in the system and this data is publically available. FDA Adverse Event Reporting System (FAERS) and the data available always require substantial duration before using and various strategies are applied for cleaning the data. European Union drug regulating authorities Pharmacovigilance (EudraVigilance) is the European data processing network management system for reporting and studying the suspected adverse reaction during new drug development.

Keywords: adverse drug reaction, pharmacovigilance, international classification of disease, FDA adverse event reporting system, eudravigilance

Abbreviation: ADR: Adverse Drug Reaction; USFDA: United States Food and Drug Administration; FDA: Food and Drug Administration; FAERS: FDA Adverse Event Reporting System; WHO: World Health Organization; PMS: Post Marketing Surveillance; ICH: International Conference on Harmonization; ICD: International Classification of Disease; ICDA: International Classification of Disease Adapted; ICPM: International Classification of Procedures in Medicines; SRS: Spontaneous Reporting System; EMA: European Medicine Agency; EU: European Union; EEA: European Economic Area; PRAC: Pharmacovigilance Risk Assessment Committee; CHMP: Pharmacovigilance Risk Assessment Committee; UMC: Uppsala Monitoring Centre; EMEA: European Medicines Evaluation Agency

Introduction

Pharmacovigilance and drug safety remains a dynamic clinical and scientific discipline. As per the World Health Organization (WHO), Pharmacovigilance may be defined as 'the science related to detection, assessment, understands and prevention of adverse effect or drug-related problems' [1]. Pharmacovigilance plays an important role in choosing a good drug for the treatment. It also plays a vital role in ensuring that doctors, together with the patient, have enough information to make a decision when needed [2]. Evidence comes to get those bigger adverse reactions which are very common, however many are preventable, disabilities, cause of illness and even death. The mechanism for monitoring and evaluating the safeties of medicine in clinical use are vital for

preventing or reduce harm to the patient. Today, Pharmacovigilance is facing a lot of challenge i.e. globalization, web-based sales and information, broader safety concerns, monitoring of establishing a product, public health versus pharmaceutical industry economic growth and perceptions to benefit and harm, outcomes, and impact and many more [3].

Role of Post Marketing Drug Surveillance in Pharmacovigilance

Post Marketing Surveillance (PMS) refers to the monitoring of the drugs when they reach the market for performing in the individuals under a wide range of circumstances. This surveillance is more likely to detect the positive and negative effects of the drugs. The post-marketing surveillance concerns with the ADR monitoring of drug in the market.

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The issues like the unapproved or off-label drug use, problems with an orphan drug, and lack of pediatric formulation, as well as issues concerning with international clinical trials in paediatrics population, are concerned with the post-marketing surveillance. The basic Pharmacovigilance Process is shown in FIGURE 1.

■ Pharmacovigilance methods as per International Conference on Harmonization (ICH) guidelines

The Pharmacovigilance methods are part of the ICH E2E guidelines. ICH E2E guidelines

specify which methods and approaches can be adopted for Pharmacovigilance study. These regulations are much clear and more specific for the study. Most recommended PASS (Post-Authorization Safety Study) are more or less embedded in the ICH E2E guidelines. FIGURE 2 depicts Pharmacovigilance Methods as per ICH guidelines [4-6].

Challenges in the Pharmacovigilance

Pharmacovigilance study can be achieved by lots of approaches and all approaches face lots of Challenges. The Challenges related to PV study are as follows

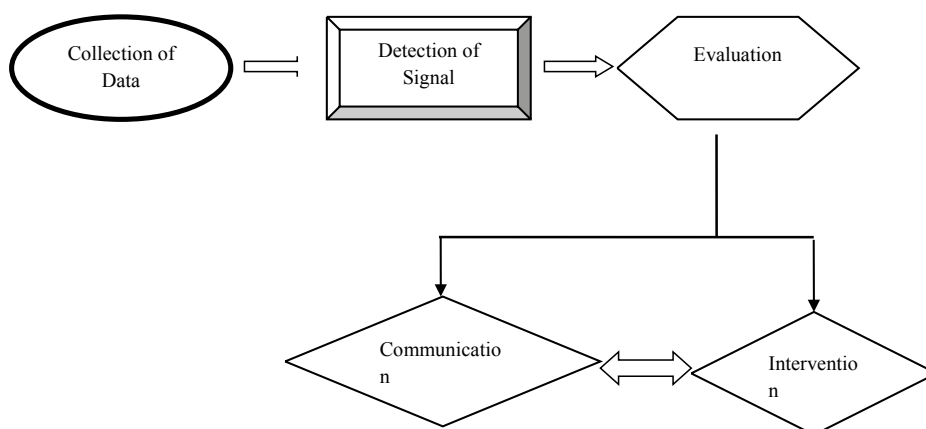


FIGURE 1. Flow chart of basic pharmacovigilance process.

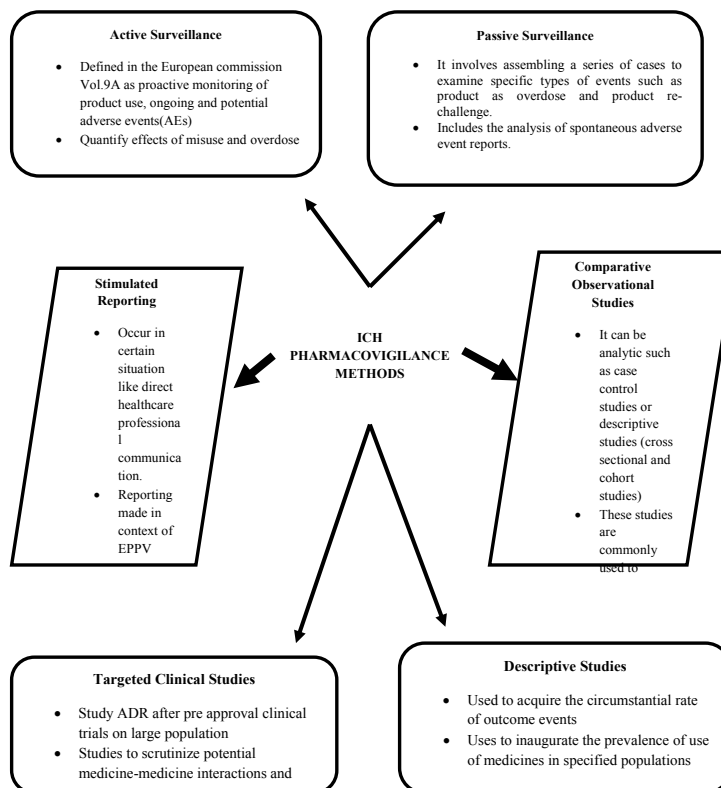


FIGURE 2. ICH methods of pharmacovigilance.

■ Globalization

It is the most important challenge during facing the Pharmacovigilance study. Today the drug distribution is very vast and increased in the exposure of a high number of populations to the large volume of medicines. These medicines include the novel chemical entity used for the symptomatic relief and lifestyle modifications as well as medicines used in developing countries to curb the disease like HIV/AIDS, malaria and tuberculosis.

■ Broader safety concerns

Today the scope of Pharmacovigilance becomes mode broaden as the wide variety of medicinal products grows nowadays. Problems are arises with the irrational use of drugs, polypharmacy, and interaction, increasing use of traditional and herbal medicines with other medicines, illegal sale of medicines and drugs of abuse over the internet increasing self-medication practices substandard medicines.

■ Web-based sale and information

This is the most important challenge toward the Pharmacovigilance. In today's era, the internet is facing the uncontrolled sale of medicines across many countries. By the use of internet drug information is provided in all forms with a different developed level of accuracy. This kind of information covers all unregistered medicines, herbal and traditional medicines with questionable safety, efficacy and quality data.

■ Pharmaceutical industry economic growth versus public health

Today all the pharmaceutical company's growth is increasing at a very large scale. Many times, Conflicting in interest within the pharmaceutical industry when dealing with public health concerns with the drug safety issues. The company needs to overcome the weakness in safety monitoring during a clinical trial and post-marketing surveillance.

■ Established products monitoring

The generic sector is the largest supplier of essential drugs all over the world. The generic sector of the pharmaceutical company has not fully recognized and its responsibility to continuously monitor the safety of its products throughout the world.

■ Outcomes and impact

With the increase in public awareness over the safety concerns of medicines, there is also increasing in a public stare on the performance of the health profession, industry and regulators. The major steps to be focused on empowering health practitioners and patients themselves with useful information that improves individuals therapy [7-9].

International Classification of Diseases (ICD)

ICD is an international tool for the "standard diagnostic tool for management, epidemiology, and clinical purposes." ICD's official name is the international statistical classification of disease and health problems [10]. ICD is maintained by WHO globally. WHO is coordinating and directing authority for health within the United Nations system [11]. The ICD is properly designed as a health care classification system and it provides a very unique system of diagnostic code for classifying the disease which includes nuanced classification of a wide variety of signs, symptoms, social circumstances complaints an external cause of injury. This ICD system is specially designed to map health conditions for the corresponding generic categories together with a specific variation. The ICD is revised periodically and is currently in its 10th revision. The ICD-11 is the final draft which is expected to be submitted to the WHO's World Health Assembly (WHA) and it has the endorsement in 2015. This version was released on 18 June 2018 [12,13].

History of ICD

Florence Nightingale proposed the international statistical congress in 1860 and this proposal resulted in the success of the first model of systematic collection of hospital data. Jacques Bertillon, a French physician intrudes the Bertillon classification of causes of death at the congress of the international statistical institute in Chicago [14,15].

In 1893, the International statistical institute adopted the first international classification edition which is known as the International List of Causes of death. The ICD had revised and published many times in a series of editions to reflect advances in health and medical sciences.

WHO was entrusted with the ICD at its

creation in 1948 and published the 6th version that is ICD-6 that incorporated the morbidity for the first time. The WHO also adopted the nomenclature Regulation in 1967.

Versions of ICD

■ ICD-6

The ICD-6 was published in 1949 was the first to become and shaped to become suitable for morbidity reporting. The combined code section for injuries and their associated accidents was split into two, a chapter for injuries, and a chapter for their external causes. Accordingly to the ICD-9 name changed from the International List of Causes of Death to International Statistical Classification of Diseases. With use for morbidity, there was a need for coding mental conditions, and for the first time, a section on mental disorders was added [16,17].

■ ICD-7

The International Conference for the Seventh Revision of the International Classification of Diseases was held in Paris under the surveillance members of WHO in February 1955. Under a recommendation of the WHO Expert Committee, this revision was limited to essential changes and amendments of errors and inconsistencies [17].

■ ICD-8

The 8th Revision Conference convened by WHO held in Geneva, from 6 to 12 July 1965. This revision was more significant than the Seventh but the basic structure was unchanged of the Classification and the general philosophy of classifying diseases, whenever possible, according to their etiology rather than a particular manifestation. "Advisory Committee to the central office on ICDA", the American Hospital Association's developed the needed adaptation that results in the publication of the International Classification of Disease, Adapted (ICDA). Beginning in 1968, ICDA-8a serves as the basis for coding diagnostic data official mortality and morbidity statistics in the United States [17,18].

■ ICD-9

The revision for the international classification of disease i.e. ICD-9 was convened by the WHO, congress held in Geneva from 30 September to 6 October 1975. In this congress, it had originally been intended for little change instead

of updating the classification. On the other end of the scale, there were many representations from countries and areas where a detailed sophisticated classification was irrelevant.

In 1978, the final proposal presented and accepted by the conference [19], which retained the basic structure of ICD. It deals with additional detail at the level of 4 digit code subcategory [20]. Publication of ICD-9 without restrictions in a world evolving electronic data system led to MeDRA [17,18].

International Classification of Procedures in Medicines (ICPM)

ICPM was developed in 1975 and published in 1978 by the WHO, this ICPM surgical procedure was created by the united states which are based on its adaptation of ICD i.e., ICDA [17,18]

■ ICD-9-CM

Clinical Modification (ICD-9-CM) was created by the U.S., the National Center for Health Statistics (NCHS). It is used in assigning the diagnostic and procedures codes associated with physician and patient office. The ICD-9-CM is purely based on the ICD-9 but it provides more morbidity detail [21,22].

It consists of two or three volumes.

1. Volume one and two contain the diagnostic code
2. Volume 3 contains the procedure code for the surgical diagnostic procedure [23]

■ ICD-10

In 1983, work on ICD-10 was begun and the new revision was endorsed by the forty-third WHA (World Health Assembly) in May 1990. The latest version of ICD-10 came into use in 1994 by the WHO member states [24]. The classification system allows more than 155000 different codes for diagnoses and procedures [25]. Several materials are made available online by WHO to facilitate its use, including a manual, training guidelines, a browser, and files for download. Some countries have adopted the international standard, such as the "ICD-10-AM" published in Australia in 1998 (also used in New Zealand) [26], and the "ICD-10-CA" introduced in Canada in 2000 [27].

■ ICD-10-CM

The adoption of ICD-10-CM was slow in

the United States. Since 1979, the US had required ICD-9-CM codes [28] for Medicare and Medicaid claims, and most of the rest of the American medical industry followed suit. On 1 January 1999, the ICD-10 (without clinical extensions) was adopted for reporting mortality, but ICD-9-CM is still using for morbidity. The U.S Department of Health and Human Services (HHS) on 21 August 2008, purpose the new codes set for reporting diagnoses and procedures on health care transactions. On 17 April 2012, the department of health human services published a new proposed rule that would rule, from 1 Oct. 2013 to 1 Oct. 2014, the compliance data date for ICD-10-CM and PCS [29].

ICD-10-CM revision includes the following:

1. Expanded injury codes
2. Relevant information for ambulatory and managed care and counter

■ ICD-10-CA

ICD-10-CA (Clinically Adapted) is a clinical modification of ICD-10 that was originally developed by the Canadian Institute of Health Information. ICD-10-CA apply beyond the scope of acute hospital care and it merely includes condition and situation which are not a disease but represents the risk factor to health such as occupational factor, psycho-social, and lifestyle circumstances [30].

■ ICD-11 (stable version for implementation release June-2018)

The international classification of disease was revised by the WHO members towards the ICD-11. Its development took place by the internet-based workspace that may be used as an evidence maintenance platform for discussion, proposals for updated of ICD. In 2019, the final draft of ICD-11 system is expected to be submitted to WHO's World Health Assembly (WHA) for official endorsement.

ICD-11 provides an implementation package that includes a translation tool, coding tool, training material and many more. These tools are accessible after self-registration form the maintenance platform [30]. Its official released can be accessed from the website www.icd.who.int.

ICD-11 includes the following specifications:

1. An organization of 30 main working groups, about 300 specialists from the 55 countries that provide their input to ICD-11 scientifically up-to-date, and structural problems apparent using ICD-10 have been solved
2. ICD-11 seems to be must easier than ICD-10. Its ontological infrastructure provides improved guidance for the user as compared to the ICD-10
3. Especially emphasis on the use of code of combination and extension codes makes the ICD more clinically relevant as compared to others
4. Especially versions, as for primary care, mental health, or dermatology are produced from the common core, the foundation
5. In the ICD-11 all the tooling produces all files and formats from the core translation tooling on the maintenance platform. ICD-11 is truly multilingual; ICD-11 has already 15 translations in progress
6. It also includes ICD entity title-fully specified Name, Textual definitions, Manifestation Properties- signs, symptoms
7. It includes Casual properties-etiology: infectious, external cause, etc., Classification properties, Diagnostic criteria

The ICD report regularly noted down the progress report of ICD revision and makes a more clear recommendation about forwarding progress in the revision [31].

Pharmacovigilance in the USA

■ USFDA

USFDA stands for the United States food and drug administration. It is the main regulatory body in the United States for the regulation of medicines. Drug safety surveillance is the most important goal of the USFDA. Spontaneous Reporting System (SRS) data, which are the mainstay of traditional drug safety surveillance, are used for hypothesis generation and to validate the newer approaches.

■ FAERS [FDA Adverse Event Reporting System (FAERS)]

FAERS is a database that contains adverse event reports, product quality complaints and medication error reports resulting in adverse events that were submitted to FDA. The database

is designed to support the FDA's post-marketing safety surveillance program for a program for drug and therapeutic biologic products. The informative structure of the FAERS data-based adhered to the international safety reporting guidance issued by the ICH E2B (International Conference on Harmonization). Medication error and adverse events are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology [32].

■ Working of FAERS

In the USA the adverse reporting system is publically available in FAERS in two different formats i.e. Extensible Markup Language (XML) and Comma Separated Values files (CSV). The data can be used by researchers which are available by FDA in legacy data form which is called LAERS data. LAERS data covers the data from January 2004 to August 27, 2012. This format of data is different from the data used now-a-days, which is called the FAERS data. In USA data present in LAERS/FAERS comprises various adverse events medication errors that were reported by healthcare professionals and consumers voluntarily. After receiving adverse reports the manufacturer should send the reports to the FDA regarding adverse events. **FIGURE 3** depicts the working of FAERS in the U.S.A.

FAERS/LAERS data files are divided into seven individual tables and this table can be manipulated directly. The main difference between FAERS and LAERS data lies in the

renaming of the keep fields: ISR and case two primary and caseid respectively.

A data set that consists of 7 data tables comprises patient Demographic and Administrative Information (DEMO), drug information, patient outcomes (OUTC), adverse events (REAC) and indications for use/diagnosis (INDI).

The quarterly data files which are available in both ASCII and SGML formats include:

1. Drug information from case reports
2. Patient outcome information from the reports
3. Demographic
4. Graphic and administrative information and the initial report image ID number
5. A "README" file containing a description of the files

The FAERS public dashboard is a highly interactive web-based tool that will allow for the querying of FAERS data in a user-friendly fashion. This tool intends to expand access of the FAERS data to the general public to search for information related to human adverse events reported to the FDA by the pharmaceutical industry, healthcare providers and consumers.

Starting June 2015, FDA is requiring that applicants electronically submit all ICSRs, ICSR establishments, and periodic safety reports. There are two options for submitting ICSRs electronically:

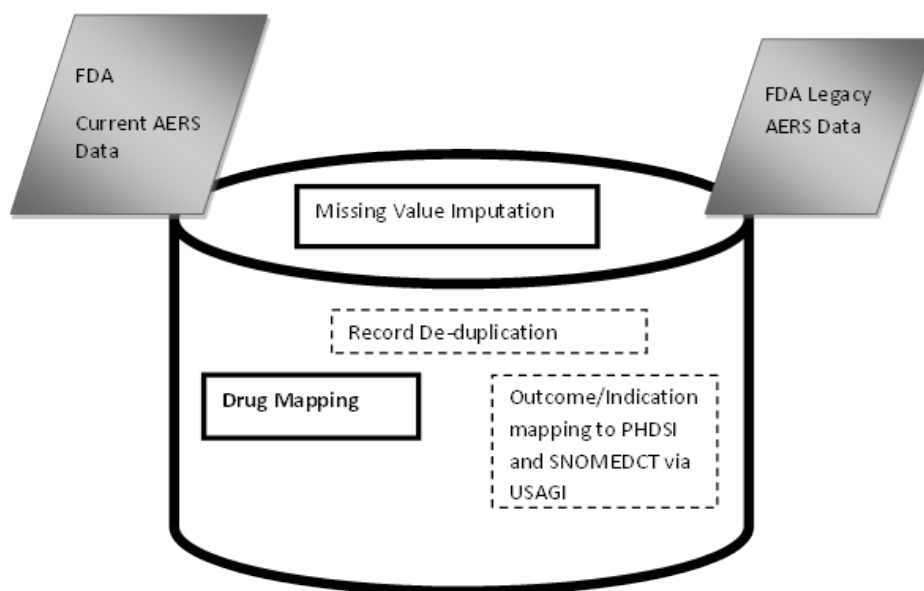


FIGURE 3. FDA Adverse Event Reporting System (FAERS).

1. Database-to database transmission (“E2B”)
2. The safety Reporting Portal (SRP) by manually entering the data via our SRP portal
3. Attachments: for both methods, we will only accept attachments in the PDF formats [33]

Usage of ICD in the United States

In the U.S.A., Public Health published the International Classification of Disease, Adapted for the Indexing of Hospitals records and Operation Classification (ICDA) which is completed in 1962 and expanding the ICD-7 in several areas to more completely meet the indexing need of hospitals. The U.S public health services latterly published the eighth revision, International classification of disease, adapted for use in the U.S. commonly referred to as ICDA-8, for official national morbidity and mortality disease. After many years, the national adaptations of the ICD-10 progress to incorporate both clinical code (ICD-10-CM) and procedure code (ICD-10-PCS) with completed revision in 2003 [25].

1. ICD-1-1900
2. ICD-2-1910
3. ICD-3-1921
4. ICD-4-1930
5. ICD-5-1939
6. ICD-6-1949
7. ICD-7-1958
8. ICD-8A-1968
9. ICD-9-1979
10. ICD-10-1999

Causes of death on United States death certificated that statistically compiled by the Centres for Disease Control and Prevention (CDCP) which is coded in the ICD and also does not include codes for human and system factors commonly called Medical errors [34,35]

Pharmacovigilance System in Europe

The EMA (European Medicine Agency) is a European Union agency that protects and evaluates medicinal products. Before 2004, it was known as the European agency for the Evaluation of medicinal products or

the European Medicines Evaluation Agency (EMA). EMA protects and promotes human and animal health by evaluating and monitoring medicines within the European Union (EU) and the European Economic Area (EEA) [36].

EMA (European Medicine Agency)

European Medicines Agency (EMA) operates the services and processes to support Pharmacovigilance in the EU and also coordinates the European Union (EU) Pharmacovigilance system. The EU Pharmacovigilance is highly advanced and comprehensive in the world and represents a transparent instrument to ensure in good level public health protection throughout the EU. It provides a unique system for monitoring the safety of medicines throughout the EU market by prevention, detection, and assessment of adverse reactions in medicine.

EudraVigilance

In the E.U, EudraVigilance is the unique system for managing and analyzing information on a suspected adverse reaction to medicine which has been authorized in the European Economic Area (EEA). EMA operates the system on behalf of the E.U medicine regulatory network [37]. **FIGURE 4** describes the activities of EudraVigilance in Europe.

Authority and Community that Involved in the Pharmacovigilance

1. Regulatory authorities which include commission, EMA and national authority
2. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC)
3. Pharmacist Doctor, Medicinal care people, and health professional
4. Pharmaceutical company

Legal Framework

In the EU, the legal framework of Pharmacovigilance is provided in regulation (EC) no 726/2004 with respect to EU authorized medicine product and in directive 2001/83/EC with respect to the national authorized medicinal product. Also of the above, commission implementing, regulation (EU) no 520/2012 outlines the practical details to be represented national competent authority and marketing authorized holder and EMA. **FIGURE 5** shows the process for authorizing the different medicinal products in EU.

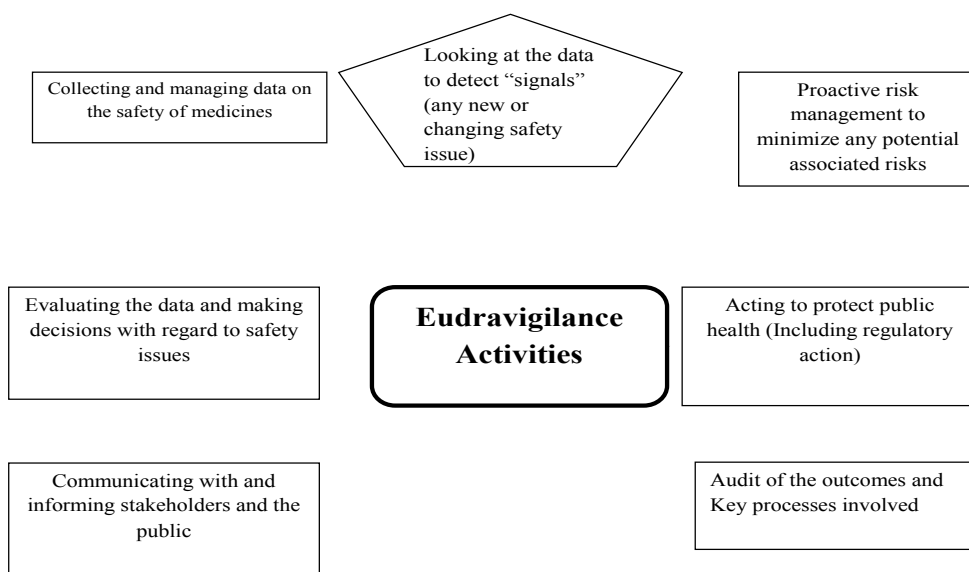


FIGURE 4. Pharmacovigilance activities of eudravigilance.

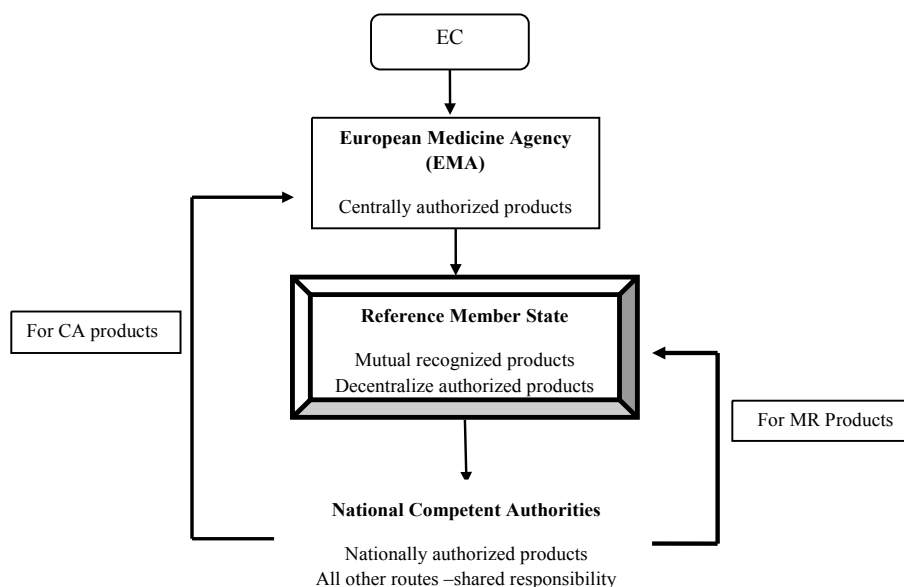


FIGURE 5. Process for authorizing the medicinal products in EU.

Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) is the main European Medicines Agency (EMA) committee which is responsible for assessing and monitoring the safety data on human medicines.

The PRAC was established in 2012 with the Pharmacovigilance legislation to help strengthen the safety monitoring of medicines across Europe.

Role of the PRAC

It is responsible for the assessment of all aspects of risk management of human medicines which includes:

1. the detection, assessment, minimization, and communication of the risk of adverse reactions
2. design and evaluation of post-authorization safety studies
3. Pharmacovigilance audit

The PRAC also provides certain recommendations on questions on Pharmacovigilance and risk management systems and also including the monitoring of their effectiveness:

1. Committee for Medicinal Products for Human Use (CHMP) for centrally authorized medicines and referral procedures
2. Coordination Group for Mutual Recognition and Decentralized Procedures-Human

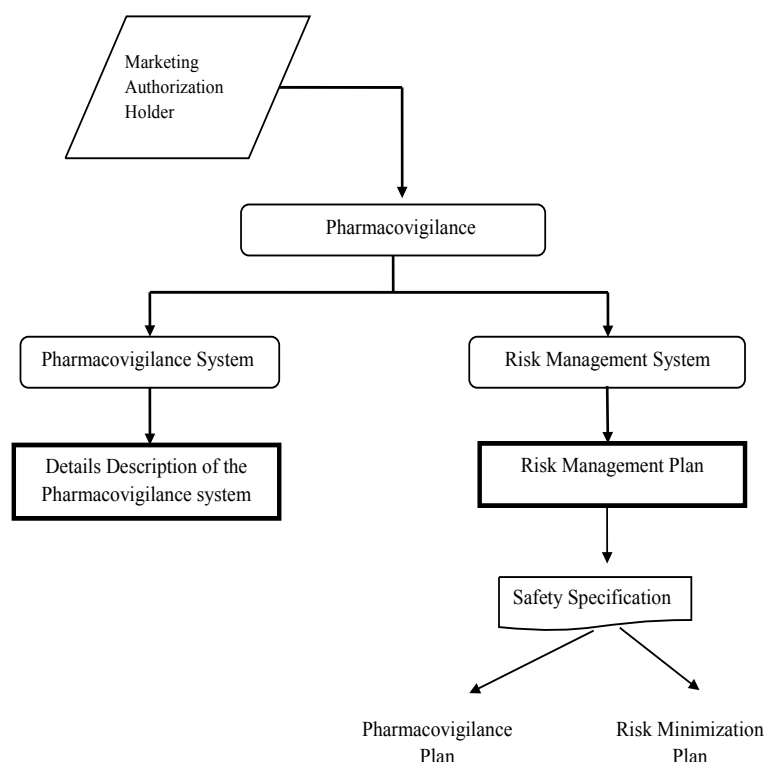


FIGURE 6. Responsibilities of PRAC.

TABLE 1. Comparison of FDA and EU pharmacovigilance.

Parameters	U.S Food and Drug Administration	EU EudraVigilance
Regulatory structure	FDA, CDER, CBER	EMA and EC
Legislation and Regulation	21 CFR §§ 314.80,314.98, 600.80	Regulation 1235/2010 and Directive 2010/84/EU111
Electronic Databases	FDA's Adverse Event Reporting System (FAERS) is a computerized information database that is designed to support FDA's post-marketing safety surveillance program for drug/biological products.	Eudravigilance Databases (Permanently accessible electronic database) for collection, collation and dissemination of information on a suspected adverse reaction to medicinal products for the human use authorized by the union.
PV Plan	In USA, PV activities(i.e, compliance with applicable post-market requirements under the FDCA and FDA implementing regulation) are applicable for most products	In Europe, ICH E2E guideline on the PV planning suggests that a ' PV plan' would be developed routinely, even when the sponsor does not anticipate that enhanced PV efforts are necessary.
Description of PV System	In accordance with CFR, which demand from the applicants having approved new drug application (NDA) or approved abbreviated new drug applications (ANDAs) and from manufacture having licensed biologic application to archive and retain records of all adverse events.	PSMF is required and is aimed to strengthen and rationalize the monitoring of safety information of medicinal products in EU market.
Risk Management System(RMS)	Application which has the approved application for the new drug or abbreviated new drug has to submit RMS. If FDA believes that the drug's benefits outweigh its risk, the manufacture have to implement RMS for the drug	Medicinal products for paediatric use and those involving a significant change in the MA, including a new manufacturing process have to implement a risk management system and all new marketing authorization application (MAA) have to contain a RMP with a detailed description of the risk management system used by the MAH.
Periodic Safety Reports	The PADERs (Periodic Adverse Drug Experience Report) shall contain among information about all serious expected and non-serious adverse events, not reported through the Post-marketingg "15-day Alert reports" or their follow-up reports	The PBRER (Periodic Benefit-Risk Evaluation Report) does not work anymore as a detailed listing of ICSRs. The submission of periodic reports is also exempted for MAHs of generic, well-established used, homeopathic or traditional-use herbal medicinal products.

(CMDH) on the use of a medicine in the Member States

3. The EMA secretariat, Management Board and European Commission, as applicable [38]

FIGURE 6 shows the basic responsibilities of PRAC.

Uppsala Monitoring Centre (UMC)

(Uppsala Monitoring Centre, SWEDEN), makes a special contribution to raising awareness with its Take & Tell campaign, publications, and training, an active presence on social media, in collaborations with patient organizations and much more. For patients you require access to the best possible information regarding your illness and possible treatments, you need to know the key questions to ask, and your health provider needs to be attentive to you and well informed. The solutions lie in open and effective communication and in the provision of comprehensive information that meets your wishes; in your asking questions and insisting you get the answers you need [39,40].

UMC is the main operational centre of the WHO programme for monitoring of drug on international level. UMC currently includes a network of Pharmacovigilance centres in near about 150 countries which represent 95% of global population. UMC provides technical support, training to country and data management tools that engage in signal analysis of new medicine-related problems. It also provides dictionaries to partners in both public and private sectors [41] (TABLE 1).

Conclusion

In this article, we have discussed the critical role

of ADR reporting in the drug post-marketing safety system. The FAERS is a database that supports the FDA'S post-marketing drug safety monitoring studies. Data available from FAERS may provide the initial signal of a safety concern that can be further investigated and there are certain limits for the data due to less information on the number of users of specific drug and inadequate case documentation. Due to these limitations and to improve information on ADR reports FDA, drug manufacturers and others are working together to achieve their goals. Thus, the essential components of ADR reporting are timely, complete, accurate and improving patient safety.

The European Medical Agency is responsible for the development, maintenance, and co-ordination of the Eudra Vigilance system, which is designed for reporting of suspected side effects. EMA'S Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for monitoring and assessing the safety guidelines for drugs used for humans. It consists of experts in medicine safety from regulatory authorities in member states, scientific experts and representatives of patients and healthcare professionals nominated by the European Commission. EudraVigilance is a system for monitoring the safety of medicines. It facilitates electronic reporting and effective analysis of suspected adverse reactions related to medicines. It helps to early detection of potential safety issues.

Conflict of Interest

The authors have none to declare.

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