Pharmacovigilance Systems and Strategies: Importance of Post-Marketing Surveillance for Ensuring Drug Safety and Patient Health in Europe, United States, and India

AMITHA SHETTY¹, AKHILESH DUBEY¹, ALAFIYA MATCHESWALA¹, and SHILPA BANGERA¹

¹Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences

February 25, 2023

Abstract

After a drug is granted a marketing license, its post-marketing surveillance is evaluated to ensure that it is continuously monitored for undesirable effects. This monitoring is achieved through an effective Pharmacovigilance system. In our review, we discuss the Pharmacovigilance systems of Europe, the United States, and India, along with several examples of effective Pharmacovigilance strategies, such as the Tracleer® Access Programme and Tracleer® Excellence programs for Bosentan, Merck’s Worldwide Adverse Experience System, the European and United States Varicella Zoster Virus Identification Programs for Varivax, the Siddha Initiative for Documentation of Drug Adverse Reaction, an android mobile app for AYUSH Pharmacovigilance, and the Global Pharmacovigilance Database by Sanofi Pasteur. This report demonstrates the importance of post-marketing surveillance in detecting rare adverse experiences that may go unnoticed during clinical trials. It also emphasizes the significance of highlighting the field of Pharmacovigilance to improve patient safety and offer them the best possible quality of life.
ABSTRACT

After a drug is granted a marketing license, its post-marketing surveillance is evaluated to ensure that it is continuously monitored for undesirable effects. This monitoring is achieved through an effective Pharmacovigilance system. In our review, we discuss the Pharmacovigilance systems of Europe, the United States, and India, along with several examples of effective Pharmacovigilance strategies, such as the Tracleer® Access Programme and Tracleer® Excellence programs for Bosentan, Merck's Worldwide Adverse Experience System, the European and United States Varicella Zoster Virus Identification Programs for Varivax, the Siddha Initiative for Documentation of Drug Adverse Reaction, an android mobile app for AYUSH Pharmacovigilance, and the Global Pharmacovigilance Database by Sanofi Pasteur. This report demonstrates the importance of post-marketing surveillance in detecting rare adverse experiences that may go unnoticed during clinical trials. It also emphasizes the significance of highlighting the field of Pharmacovigilance to improve patient safety and offer them the best possible quality of life.

Keywords: Post-marketing surveillance, Pharmacovigilance system, Bosentan, Varivax, SiddAR.

KEY POINTS

- Post-marketing surveillance is critical to continuously monitor drugs for undesirable effects that may have gone unnoticed during clinical trials.
- An effective Pharmacovigilance system is necessary to ensure patient safety and improve their quality of life.
- The review discusses the Pharmacovigilance systems of Europe, the United States, and India, along with several effective Pharmacovigilance strategies.
- The report emphasizes the importance of highlighting the field of Pharmacovigilance to improve patient safety and offers them the best possible quality of life.
- The examples of effective Pharmacovigilance strategies presented in the review provide insights and guidance for developing more efficient Pharmacovigilance systems.

INTRODUCTION

Medicines play an important role in addressing health problems. However, despite all their benefits, adverse drug reactions (ADR) remains a common, yet the primarily unavoidable cause of illness and have been ranked as the top 10 leading causes of mortality. Although drugs are approved for marketing only after assessing their safety and efficacy through clinical trials, there are circumstances wherein unanticipated adverse reactions can arise, and therefore Post-Marketing Surveillance (PMS) remains a crucial aspect in monitoring ADRs. PMS involves monitoring the safety of the drugs in a larger pool of individuals, including various age groups and special populations. It is essential to have mechanisms in place to monitor and evaluate the safety and effectiveness of medicines in clinical use to avoid or mitigate risks to patients and improve public health[1].

Pharmacovigilance, an umbrella term for monitoring, reviewing, and analyzing ADRs, is part of effective drug regulation systems, clinical practice, and health programs conducted for the public. WHO defines Pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems” [2]. Its objective is to improve patient care and safety and aid public health/support programs by providing reliable, accurate, and balanced information to practically evaluate the benefit-risk profile of medicines and vaccines. In simple terms, Pharmacovigilance can be termed as the branch of health care that seeks to make the safest possible use of medicines by identifying
the risks and the risk factors in the shortest possible time so that harm can be avoided or minimized. There are currently 79 national centers under the stimulus and collaboration of the World Health Organization (WHO) and its Collaborating Centre for International Drug Monitoring (The Uppsala Monitoring Centre). This is the world’s largest database of ADR reports and is a prime source for generating signals of previously unrecognized ADRs [3].

NEED FOR SETTING UP A SYSTEM OF PHARMACOVIGILANCE

It is imperative to have an effective drug monitoring system for all drugs. Different tragedies, such as the thalidomide disaster, which are the repercussions of failure to have a proper risk management plan, have brought this importance to light, and this has also given us lessons in having effectively efficient systems for drug safety and control.

The critical goals of the pharmacovigilance system are as follows[4]:

- Improving treatment for patients and safety while using pharmaceutical products in surgical and paramedical procedures;
- Improving the health of the public and providing safety and protection concerning the utilization of pharmaceutical products;
- Contribute to the evaluation of the benefit, harm, efficacy, and risks associated with the medicinal products, promoting their healthy, fair, and more productive use;
- Promoting pharmacovigilance education, knowledge, clinical training, and communication of this information to the HCPs, patients, and consumers.

Benefits and risks are the two phases of the same coin. However, it is always necessary to deliver a drug product whose benefits outweigh the risks to patient safety in the context of drugs. To ensure this, various countries have undertaken risk management plans and safety reporting programs to allow early detection, assessment, remedies, and measures to be taken to reduce or complete eradication of risks that have been reported. Drug overdose, drug-drug interactions, lack of efficacy, suspected pharmaceutical defects (spurious and adulterated drugs), resistance, and medication errors should all be included in the reporting of ADRs [5].

PHARMACOVIGILANCE IN EUROPE

The European Medicines Agency (EMA) is the main European body responsible for pharmacovigilance in Europe. To evaluate and monitor the safety and effectiveness of the medicines, the EMA has constituted a committee known as the Pharmacovigilance Risk Assessment Committee (PRAC). EudraVigilance is among the main components of the European Strategy for Risk Control to improve pharmacovigilance efficiency in the EMA[6].

Practical Implementation of Pharmacovigilance in Six Member States:

United Kingdom:

United Kingdom follows a centralized system of pharmacovigilance with the Medicines and Healthcare Products Regulatory Agency (MHRA) being the main regulatory body for all medicines at its core. ADRs are collected in the MHRA database through the Yellow Card Scheme. This Scheme includes both synthetic and biological products. In 2015, the MHRA also launched the “Yellow Card App” for smartphones. MHRA processes an enormous number of ADR reports due to which there is no thorough assessment of reports when compared to the pharmacovigilance systems in the other states[7, 8].

Finland:

The Finish Medicines Agency (FIMEA) is responsible for the collection and evaluation of the ADR reports and is the key actor in the Finish ADR reporting system. Regular emails or downloading and submitting the completed form on the FIMEA’s homepage are the two ways via which physicians and pharmacists can report the ADRs. Access to FIMnet is a requirement in case of electronic reporting by healthcare professionals and
pharmacists. On completion of the evaluation, the attributes of the ADR reports are forwarded via regular mail to the respective MAH, EMA, and WHO. This activity is carried out by the FIMEA[9, 10].

Poland:
The Polish National Competent Authority responsible for the collection and assessment of all the submitted ADR reports is the Office of Registration of Medicinal Products, Medical Devices, and Biocidal Products (URPL). The patients have three options for reporting: 1) inform a healthcare professional 2) inform the Marketing Authorization Holder (MAH), and 3) report the ADR via e-mail, fax regular mail, or online directly to the URPL office. On receiving the ADR reports, a causality assessment of the reported incidents is carried out by the national competent authority URPL. These are further evaluated scientifically to detect the signals and are then forwarded to the EudraVigilance as well as the WHO database.

France:
A decentralized network of Centres Regionaux de Pharmacovigilance (CRPVs) and the national competent authority, Agence Nationale de Securite de Medicament et des Produits de Sante (ANSM) composes the pharmacovigilance system in France. Collection and validation of data are done by CRPV and ANSM which is responsible for the validation of the data as well as an overall decision-making process. The marketing authorization holders can report directly to the ANSM. ADRs suspected by a patient can be reported directly to the ANSM by fax, mail, and via an online form or the patient can also directly contact the marketing authorization holder or even seek the advice of a healthcare professional. These reports are evaluated by the regional CRPVs’ pharmacovigilance units after which the verified reports are entered into the French pharmacovigilance database (FPD). When deemed necessary, the findings are forwarded to the EMA and WHO’s international database [11].

Portugal:
The national competent authority of Portugal is the National Authority of Medicines and Health Products (Autoridade Nacional do Medicamentos e Produtos de Saude, I.P., or INFRAMED). It is in affiliation with the National Health Ministry which is in charge of legislative matters[12, 13]. Portuguese pharmacovigilance is based on the four regional centers. This is consistent with the administrative regions of Portugal, i.e., North, Lisbon, Centre, and South. These centers in collaboration with the INFARMED collect process and evaluate the ADR reports. ADR reports are submitted by the Healthcare professionals and the Patients via online forms, email, fax, or regular mail, while the reports of ADR by the marketing authorization holders are directly submitted to INFARMED. A comprehensive causality assessment shall be carried out by the regional centers within 30 days from the reporter’s submission before forwarding it to INFARMED[14].

Germany:
The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, or BfArM) centrally collects the ADRs related to synthetic medicines and the Federal Institute for Vaccines (Paul-Ehrlich-Institut, or PEI) is the Institute for reporting of the ADRs resulting from biological[15]. Reports of ADRs are submitted by the Physicians to the Drug Commission of the German Medical Association (Arzneikommission der deutschen Ärzteschaft, or AkdÄ), pharmacists can submit the ADR reports to the largest national association of pharmacists, the Drug Commission of the German Medical Association (Arzneikommission der deutschen Ärzteschaft, or AkdÄ) through regular mail or fax. Finally, the reports are collected centrally and saved in pseudonymized form by the BfArM and then forwarded to the respective MAH, EMA, and WHO. For biologics, the healthcare professionals submit the ADR reports to the state health authorities (Gesundheitsämter der Länder). ADR report evaluation is carried out within the AkdÄ and AKM pharmacovigilance units. A software program known as ARTEMIS (Adverse Drug Reactions Electronic Management and Information System) carries out the evaluation and signal detection [16, 17].

A comparison of the pharmacovigilance system in the six member states of the EU is given in table 1.
<table>
<thead>
<tr>
<th>United Kingdom</th>
<th>Finland</th>
<th>Poland</th>
<th>France</th>
<th>Portugal</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervision</td>
<td>Centralized</td>
<td>Centralized</td>
<td>Centralized</td>
<td>Decentralized</td>
<td>Centralized</td>
</tr>
<tr>
<td></td>
<td>Department of Health</td>
<td>Ministry of Social Affairs and Welfare</td>
<td>Health</td>
<td>Ministry for Health and Social Security</td>
<td>National Health Ministry</td>
</tr>
<tr>
<td></td>
<td>MHRA</td>
<td>Fimea</td>
<td>URPL</td>
<td>ANSM</td>
<td>INFARMED</td>
</tr>
<tr>
<td>National Competent Authority</td>
<td>Professionally obliged</td>
<td>Obligated in case of vaccines</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
</tr>
<tr>
<td>Reporting Healthcare professionals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Professionally obliged</td>
</tr>
<tr>
<td></td>
<td>Report via YCS system to MHRA</td>
<td>Report synthetic products to Fimea and vaccines to THL</td>
<td>Report to URPL</td>
<td>Report to ANSM’s regional units</td>
<td>Report to INFARMED’s regional units</td>
</tr>
<tr>
<td>Reporting patients</td>
<td>Voluntary</td>
<td>Voluntary</td>
<td>Voluntary</td>
<td>Voluntary</td>
<td>Voluntary</td>
</tr>
<tr>
<td></td>
<td>Since 2005</td>
<td>Since 2012</td>
<td>Since 2012</td>
<td>Since 2011</td>
<td>Since 2013</td>
</tr>
<tr>
<td></td>
<td>Report to HCPs, MAHs or via YCS system to MHRA</td>
<td>Report to HCPs, MAHs or Fimea</td>
<td>Report to HCPs, MAHs, ANSM or regional units</td>
<td>Report to HCPs, MAHs, INFARMED or regional units</td>
<td>Report to HCPs, MAHs, or BfArM/PEI</td>
</tr>
<tr>
<td>Reporting Marketing Authorization Holders</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
<td>Legally obligated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Report to MHRA database</td>
<td>Report to Fimea</td>
<td>Report to URPL</td>
<td>Report to ANSM</td>
<td>Report to INFARMED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Report to BfArM/PEI</td>
</tr>
<tr>
<td>Evaluation and signal detection</td>
<td>Fimea</td>
<td>URPL</td>
<td>Regional units</td>
<td>Regional units</td>
<td>AkdÅ, AKM, BfArM, PEI</td>
</tr>
</tbody>
</table>

**Table 1:** Comparison of the national pharmacovigilance systems [17]

**Post-Marketing Pharmacovigilance Strategies Adopted by Pharmaceutical Industries in Europe:**

TRACLEER ® EXCELLENCE (TRAX PMS) SYSTEM FOR BOSENTAN:
TRAX PMS is a prospective, internet-based, non-interventional, European post-marketing surveillance database. The physicians prescribing Bosentan in the EU were encouraged to take part in TRAX PMS to ensure the physicians understood the risks associated with Bosentan. Once the prescribers undergo registration as TRAX PMS users, are required to enter all the patient data into the system regularly [18] (Fig. 1).

**SPMSD AE DATABASE AND EU VZVIP FOR VARIVAX®:**

Sanofi Pasteur MSD (SPMSD) implemented The European Varicella Zoster Virus Identification Program (EUVZVIP) to test samples causing specific adverse drug events to distinguish between the existence of wild-type and vaccine strains. It is an internal service provided by the SPMSD to the HCPs who report the AE’s in individuals receiving the Oka/Merck Varicella vaccine[20].

**PHARMACOVIGILANCE IN UNITED STATES**

The Elixir tragedy of 1937 and the Thalidomide tragedy of 1960 revised the Food and Drug Administration (FDA) regulation for demonstrating the safety and effectiveness of the drug before issuing the marketing authorization[21]. Pharmacovigilance is regulated by FDA with the help of the Centre for Drug Evaluation and Research (CDER) and the Centre for Drug Evaluation and Research (CBER)[22]. Information on adverse events and medication error reports submitted to FDA are captured in the FDA Adverse Event Reporting System (FAERS) database. FAERS is intended to aid the post-marketing surveillance program for the safety of drugs and biologicals for therapeutic use. The informatics framework of the FAERS database reflects the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B)[23]. This serves as a computerized database and repository for adverse events and medication errors for all the drugs that are being marketed in the United States[24]. The coding of all the adverse effects and medication effects is done in terms of Medical Dictionary for Regulatory Activities (MedDRA) terminology. FDA has set up a medical product safety reporting program for health professionals, patients, and consumers known as MedWatch.

Reporting of ADRs by Health professionals, patients, and consumers to FAERS can be done in two ways[25] (Fig. 2):

a) Directly to the FDA via MedWatch: the following methods can submit the voluntary report[27]:

1. Fill the Form 3500, which is available online at: www.accessdata.fda.gov/scripts/medwatch;
2. Call 1-800-FDA-1088 - for reporting via telephone;
3. Fill in the downloaded copy of Form 3500 available from the following website: www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM82725.pdf this can then be faxed to 1-800-FDA-0178 or can be mailed back as well (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787) using the addressed form, which is postage-paid[28].

**NOTE :** Voluntary reporting of ADR by consumers and health care professionals is done via FDA form 3500B and mandatory reporting for regulated industries and user facilities are done via FDA form 3500A[29].

b) Reporting to the manufacturer, who then reports to the FDA: The manufacturer’s website contains the contact information used to report the adverse effects, and a majority of reports are obtained since this seems to be an easier way of reporting from the manufacturer consumer’s view. The manufacturer collects all the required information from the report and submits the same to the FDA. In the case of periodic reporting, the manufacturer can submit the reports to the regulatory authorities through periodic safety reports, which contain the compendium of all ADR reports obtained over a given period[28].

Based on the safety and impact of the ADRs on public health, the FDA enters the reported adverse effect into the FAERS database after a thorough assessment and screening of the ADRs. Based on the safety reports received FDA takes the following possible actions:

- Request Labeling Changes
- Enhance Education
- Send safety alerts
• Request drug product removal from the market
• Pharmacovigilance, more studies or more trials
• Request change to design, packaging, and manufacturing
• Request Medication Guide
• Request for a Risk Evaluation and Mitigation Strategy (REMS) – Communication plan, restricted use

The Sentinel Initiative was introduced by the FDA under the US FDA Amendments Act of 2007 for the submission of adverse events mandatory for the manufacturers[30].

Post Marketing Pharmacovigilance Strategies Adopted by Pharmaceutical Industries in the United States:

TRACLEER ACCESS PROGRAMME (T.A.P) FOR BOSENTAN:

Bosentan is available only through controlled distribution in the US, i.e., Tracleer Access Programme (T.A.P). Bosentan is prescribed to a patient only after the physician and the patient under therapy are registered with a duly signed form as consent[31]. A written certificate must be issued by the physician stating that:

• The patient is diagnosed with PAH and Bosentan is prescribed in a medically appropriate manner
• The physician has prescribed the drug only after reviewing the hepatic and pregnancy warnings with the patient.
• The physician has agreed for taking up the liver function and pregnancy tests.

Under T.A.P, the distributor of Bosentan is required to call the patient once a month to ensure the liver function and pregnancy tests is conducted every month. The sponsor summarizes the findings of this surveillance and submits them to the FDA on an annual basis. This summary includes monitoring the liver function tests and the exposure of the fetus to the drug[32].

MERCK’S WORLDWIDE ADVERSE EXPERIENCE SYSTEM (WAES) AND UNITED STATES VARICELLA ZOSTER VIRUS IDENTIFICATION PROGRAM (VZVIP) FOR VARIVAX®:

To observe if VZV is in conjunction with particularly adverse effects in the Oka/Merck vaccines or vaccine contacts, and to decide if the recorded events are consistent with wild-type vaccines, Merck implemented The Varicella Zoster Virus Identification Program in the US, known as US VZVIP. Merck’s Worldwide Adverse Experience System (WAES) database includes documentation of AEs randomly reported by the HCPs, patients, and customers to the company and case reports from the literature published. All the reports from WAES are entered into Vaccine Adverse Event Reporting System (VAERS), which the FDA manages[33].

PHARMACOVIGILANCE IN INDIA

India is the second most popular country with various ethnicities, and a wide range of disease recurrence sequences it is certainly important to have a unified pharmacovigilance system across the country[34]. Under the supervision of the Drug Controller of India, a formal ADR monitoring system has been established in the year 1986, with 12 regional centers[35]. India joined the WHO program for International Drug Monitoring by the Uppsala Monitoring Committee in 1997, with six regional centers, identifying the center in New Delhi as the national center[36]. In the year 2005, the National Programme of Pharmacovigilance came into existence, and this was later called the Pharmacovigilance Programme of India (PvPI) in 2010. As part of PvPI, New Delhi has chosen the All India Institutes of Medical Sciences (AIIMS) as the National Coordinating Centre (NCC) to safeguard public health by-product protection validation. The Central Drug Standard Control Organization (CDSCO), headquartered in New Delhi, regulates PV activity in India. To ensure accurate reporting of ADR’s regional, zonal, and peripheral ADR reporting centers have been established by the PvPI (Fig. 3). Suspected ADR Reporting Form has been provided on the official website of the Indian Pharmacopoeia Commission (www.ipc.gov.in).

The Vigi-flow software collects and processes all the ADRs that have been reported at respective centers. Vigi-flow is maintained by UMC in Uppsala, Sweden, and is by the ICH EB Standard[38]. The associate identifies a signal at these centers, then submits it to CDSCO and the World Health Organization (WHO)
for further regulatory intervention. CDSCO-WHO expresses its decision independently or in partnership through a newsletter, internet, publication, or official website supporting public health [39] (The process of ADR reporting in India is shown in Fig. 4).

The NCC-PvPI collaborated with the WHO-UMC to engage in the International drug monitoring program. The software’s like this:

- Vigiflow: internet-based ICSR managing system for international drug monitoring
- Vigibase: WHO database for global ICSR
- Vigimine: new development of Vigisearch for the comparison of statistical data
- Vigimed: part of the UMC collaboration portal
- Vigilize: a tool that provides access to ICSRs in Vigibase

These are provided by WHO-UMC to achieve the objective of PvPI in a more efficient way. India has become the first country to report over one lakh ICSRs to Vigiflow[39]. Several drugs are scanned under the PvPI, and the HCP receives quarterly drug safety alerts on Suspected Unexpected Serious Adverse Reactions [SUSARs] via newsletters[35]. Hemovigilance was adopted as an integral part of PvPI which helped in monitoring the ADRs and their occurrence in blood product administration as well as blood transfusion. Different multinational companies have started outsourcing PV activity in India fostering a positive Pharmacovigilance culture[41].

**Post Marketing Pharmacovigilance Strategies Adopted by Pharmaceutical Industries in India:**

**SIDDHA INITIATIVE FOR DOCUMENTATION OF DRUG ADVERSE REACTION (SIDDAR): ANDROID MOBILE APP FOR AYUSH PHARMACOVIGILANCE PROGRAMMES IN INDIA:**

While there is no technical word for Pharmacovigilance in the Siddha literature, the idea of Pharmacovigilance is vividly present. Pharmacovigilance includes drug and therapeutic procedures, i.e., Varmam and Thokkanam, Karanool, and Detoxification procedures in Siddha[42]. The Nanju Murivu Nool, a classic textbook of Siddha, describes the adverse reactions to medicines and food when they are prepared or used inappropriately[43].

To implement the pharmacovigilance program for ASU and H Drugs, the All India Institute of Ayurveda, New Delhi, is the National Pharmacovigilance Coordination Centre (NPvCC). The NPvCC, in consultation with the Pharmacopoeia Commission of Indian Medicine and Homoeopathy (PCIM&H), shall undertake the Causality Assessment of the signals received from the IPvCs. For real-time documentation, minimizing time consumption, and encouraging the practice of being careful about medications on the market, SiddAR App was introduced. The HCP, patients, and consumers can report the ADR via this app. For the completion of ADR reporting, the user must fill out the details in the appropriate fields and then submit the ADR form by e-mail. Staff will follow up on the recorded ADR for further review. Even though it is in the Siddha domain, it can be personalized and conveniently converted to other AYUSH streams such as Ayurveda, Unani, and Homeopathy[44].

**SANOFI PASTEUR GLOBAL PHARMACOVIGILANCE DATABASE FOR A (AB') 2 PERIG:**

FAVIRAB F(ab’)2 fragments of equine anti-rabies immunoglobulin is an immunoglobulin specific to rabies. FAVIRAB is indicated for post-exposure prophylaxis of rabies in all subsets of the pediatric population and in adults suspected of being exposed to the rabies virus. As per SmPC, FAVIRAB must be administered only under medical supervision. It must only be used in combination with the rabies vaccine, as recommended by the WHO Specialist Consultation on Rabies. However, where HRIG is inaccessible, F(ab’)2 PERIG should be administered without hesitation to avoid and treat anaphylactic reactions under close medical supervision. In the event of these reactions, further administration of F (ab’) 2 pERIG should be immediately withheld, and appropriate medication has to be given for the initiated reaction. Since Favirab is of heterologous (non-human origin) nature, the risk of anaphylactic-type undesirable effects should continuously be assessed before administration[45].
Sanofi Pasteur maintains a global pharmacovigilance database for F(ab’)2 PERIG for all the AE’s concerning FAVIRAB. Records of adverse outcomes from multiple outlets, including weekly literature reviews and random reports from health practitioners, health agencies, or patients, as well as submitted reports of adverse events from clinical trials funded by Sanofi Pasteur, are all recorded and maintained in Sanofi Pasteur’s Global Pharmacovigilance database for F(ab’)2 PERIG.

The comparison between the EU, US, and Indian Pharmacovigilance systems is summarized in table 2.

<table>
<thead>
<tr>
<th></th>
<th>Europe</th>
<th>US</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Authority</strong></td>
<td>EMA</td>
<td>FDA</td>
<td>CDSCO</td>
</tr>
<tr>
<td><strong>Regulatory Authority for</strong></td>
<td>EVDAS</td>
<td>CDER and CBER</td>
<td>NCC, PvPI, IPC</td>
</tr>
<tr>
<td><strong>Pharmacovigilance Guidelines</strong></td>
<td></td>
<td>Good Pharmacovigilance Practices</td>
<td>Schedule Y of Drugs and Cosmetics Act</td>
</tr>
<tr>
<td><strong>ADR Reporting Database</strong></td>
<td>EudraVigilance, European Database of Suspected Adverse Drug Reactions Reports, EVDAS, EVWEB</td>
<td>MedWACTH FAERS</td>
<td>Vigiflow, Vigibase</td>
</tr>
<tr>
<td><strong>Types of different ADR reporting form</strong></td>
<td>Three 1. ICSR form level 1 if the MAH does not have a product for the specific substance 2. ICSR form level 2a if the MAH has a product for the specific substance 3. ICSR form level 3 if the case has been previously submitted by the MAH and for the MLM cases</td>
<td>Three 1. Form 3500 2. Form 3500A 3. Form 3500B</td>
<td>Two 1. Suspected ADR reporting form for Healthcare personnel 2. Medicines side effect reporting form for consumers</td>
</tr>
<tr>
<td><strong>PSUR submission</strong></td>
<td>To PSUR repository</td>
<td>To CDER for drug products and CBER for biological products</td>
<td>To DCG (I) and PvPI</td>
</tr>
<tr>
<td><strong>Periodic safety reports</strong></td>
<td>PBRER First 2 y - every 6 mo, once a year for the 2 consecutive years, once in 3 y thereafter</td>
<td>PADERs 15-d alert reports, quarterly for first 3 y, and annually thereafter</td>
<td>PSUR First 2 y - every 6 mo Once a year for the 2 consecutive years</td>
</tr>
<tr>
<td><strong>Risk management system</strong></td>
<td>ERMS</td>
<td>REMS</td>
<td>Pharmacovigilance guidance document for all MAHs of Pharmaceutical Products</td>
</tr>
</tbody>
</table>

Table 2: Comparison between EU, US, and Indian Pharmacovigilance

(Abbreviations: CBER, Centre for Biologics Evaluation; CDER, Centre for Drugs Evaluation and Research;
CDSCO, Central Drugs Standard Control Organization; FAERS, FDA Adverse Event Reporting System; MAHs, Market Authorization Holders; EVDAS, EudraVigilance Data Analysis System; EVWEB, EudraVigilance WEB trader; ICSR, Individual Case Safety Report; PBRER, Periodic Benefit Risk Evaluation Report; PADERs, Periodic adverse drug experience reports; PSUR, Periodic Safety Update Report; ERMS, European Risk Management Strategy; REMS, Risk Evaluation and Mitigation

CONCLUSION

Underreporting of adverse events is one of the significant global setbacks. Although the drug has been introduced into the market only after its safety and efficacy have been approved, it is important to recognize that the risks involved with the drugs come to light only when the drug is introduced into the market. This is because clinical trials used to prove the safety and efficacy involve strict inclusion and exclusion criteria which restrict the study of drugs in special age groups like children, elderly as well as pregnant women that are usually not analyzed during the clinical trials; factors that result in reactions caused by a drug like the drug-drug interactions, generic as well as environmental factors. This demands the need for Post-marketing Pharmacovigilance.

When the drug is introduced into the market, it is used in a large population for a more extended period and used the drug in patients with different characteristics. This helps to identify the unidentified AEs. This report demonstrates how post-marketing surveillance can be used to identify and evaluate those rare adverse experiences that might not be observed during the clinical trials and also shows the importance of making every effort in highlighting the field of pharmacovigilance to improve the safety and improve their quality of life of patients. This article gives a glimpse of specific Pharmacovigilance strategies adopted across the globe that helps in securing early identification of new adverse reactions or highly susceptible subgroups of patients, and the implementation of such steps to mitigate those risks. Therefore, if adverse effects and drug toxicities occur, it is essential to ensure that they are reported, analyzed, and communicated to the general public to interpret the information.

REFERENCES

12. European Medicines Agency. Good pharmacovigilance practices. [Internet]. [Cited on 23 Sep 2021].


22. Akst J. Sulfanilamide tragedy. The Scientist. June 2013. [Internet] [Cited on 21 Sep 2022].

23. US Food and Drug Administration. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. [Internet] [Cited on 21 Sep 2022].

24. US Food and Drug Administration. FDA Adverse Event Reporting System [Internet] [Cited on 15 Jan 2022].

25. FDA. Med Watch: the FDA Safety Information and Adverse Event Reporting Program. [Internet] [Cited on 22 Sep 2022].

26. Cobert B. FDA and PBRERs (PSURs). C3i Solutions. 2013. [Internet] [Cited on 23 Sep 2022]

27. US Food and Drug Administration System. An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System. [Internet] [Cited on 15 Jan 2022].


31. FDA. Adverse Event Reporting System (AERS). [Internet] [Cited on 22 Sep 2022].


36. US Food and Drug Administration. Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER - How Postmarketing Reports Get to FDA. [Internet] [Cited on 15 Jan 2022].

37. Gupta YK. Pharmacovigilance Programme for India. [Internet] [Cited on 23 Sep 2022].

38. Uppsala Monitoring Committee. Vigiflow. [Internet] [Cited on 23 Sep 2022].
44. Aayushsuraksha. Hierarchy of Pharmacovigilance Program. [Internet]. [Cited on: 02 Feb 2022].

Fig. 1: Data reconciliation process between TRAX PMS and Actelion Global Drug safety database[19]

Fig. 1: Reporting of ADE’s to FAERS
Fig. 2: Reporting of ADRs by Health professionals, patients, and consumers to FAERS[26]

Fig. 3: ADR Reporting Zones in India[37]

Fig. 4: Process of ADR reporting in India[40]