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PHARMACOVIGILANCE: A NEW ADVERSE DRUG REACTIONs TOOL

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ABSTRACT

Pharmacovigilance is a pharmacological science that relates with drug safety. It relates to the *collection, assessment, monitoring* and *prevention* of Adverse Drug Reactions (ADRs) caused by any type of pharmaceutical products.[1] The World Health Organization (WHO) defines Pharmacovigilance as *"the study of activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem" (WHO 2004).* After the disaster of Thalidomide in 1961, the WHO has established a Programme for International Drug Monitoring.[2] The main Aim of Pharmacovigilance Programme is to ensure the safety of public for use of medicines. Pharmacovigilance is needed to ensure the safety of medicines. The scope of pharmacovigilance is to monitoring continuously of any Adverse Drug Reactions. To reassess and update the *Benefit/Risk* ratio profile of any drug through the Periodic Safety Update Reports (PSURs).[3] Government of India started the Pharmacovigilance Program of India in July 2010 at All India Institute of Medical Sciences (AIIMS), New Delhi. It was the National Coordinating Centre (NCC) for monitoring of adverse drug reactions until it shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad in April 2011. The objective of PvPI is to create a national system for the safety of patients and to analyse any new signals from reported cases. It analyses the *Benefit/Risk* ratio of marketed formulations, and generate evidence-based information on safety of medicines. Adverse Drug Reaction is a response to a drug, which is noxious and unintended. It occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. Causality Assessment is a method used to evaluate a relationship between a drug exposure and the occurrence of the Adverse Drug Reactions. Clinician, pharmacists, pharmaceutical industry and healthcare professionals can do it.[4] Signal is defined as "*Reported information on a possible causal*

relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously".

KEYWORDS: Adverse Drug Reactions, Thalidomide, Pharmacovigilance, PSUR, NCC-PvPI, Causality Assessment, Signal.

INTRODUCTION

Drug Discovery is a very complicated process and it requires multiple steps including *Pre-Clinical studies* and *Clinical Trials*. The Researches now a day focus on making a drug safer for the consumer. For this, they require various phases in Clinical Trials. The first three phases are testing the Active Pharmaceutical Ingredient (API) in the Laboratory, but the Phase IV studies includes the Post-Marketing Surveillance *i.e.* watching the use of drug in public. In this, the drug is Monitored and Reported for any known or unknown Adverse Drug Reactions (ADRs) and Adverse Drug Events (ADEs); this process is called as Pharmacovigilance.[5]

Pharmacovigilance is a pharmacological science that relates with drug safety. It relates to the *collection, assessment, monitoring* and *prevention* of Adverse Drug Reactions (ADRs) caused by any type of pharmaceutical products.[6] The word Pharmacovigilance is derived by two words namely: *Pharmakon*, which is Greek word for "Drugs" and *Vigilare*, which is a Latin word, means "To Keep Watch". It is the practice of monitoring the effects of Pharmaceutical products after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions.

The World Health Organization (WHO) defines Pharmacovigilance as *"the study of activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem" (WHO 2004).* After the disaster of Thalidomide in 1961, the WHO has established a Programme for International Drug Monitoring.[7] The aims of Pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.[8] WHO started the Programme for International Drug Monitoring in 1968 with Uppsala Monitoring Centre (UMC) in Sweden. Communication of safety signals recognised through analysis of global data of this Adverse Drug Reactions (ADR) is the main function of this co-ordinating centre. This initiative has gained international acceptance, with a total of 156 countries

currently being the part of the programme, contributing 1.5 crore ADR reports in Vigibase, an ADR database.[9] Now it include the Herbal drug products, Traditional and Complementary medicines, Blood products, Biologicals, Medical devices, and Vaccines. In addition, it possesses various roles such as identification, quantification, and documentation of drug-related problems that are responsible for drug-related injuries.[10]

Terminologies Used In Pharmacovigilance

Pharmacovigilance is a branch that got its own terminology, which is very important to understand.

1. **Absolute Risk**: The probability of an event-affecting member of a particular population (*e.g.*1 in 1,000).
2. **Attributable Risk:** Difference between the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk); the difference from the absolute risk in the probability of an event happening, attributable to a drug or other variable.
3. **BENEFIT-RISK:** 'Benefit-risk' is a logically mismatched pair, the more accurate, benefit-harm is preferable.
4. **ADR (Adverse Drug Reaction):** It is a non-intended reaction to the drug occurring when there is a direct causal relationship between the drug and the reaction, have been proven.
5. **ADE (Adverse Drug Event):** It is a side effect, which occur with a drug, and its causal relationship with the drug is not known.
6. **Causal Relationship:** It occurs when a drug is thought to be responsible for the occurrence of Adverse Drug Reactions.
7. **Implied Causality:** It refers to spontaneously reported AE cases where the causality is always presumed to be positive unless the reporter states otherwise.
8. **Incidence:** Number of new cases of an outcome, which develop over a defined time in a defined population at risk.
9. **Individual Case Safety Report (Icsr):** Reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more medicines. These have also been referred to as adverse drug reaction (ADR) reports or adverse event (AE) reports.
10. **Prevalence:** Number of existing cases of an outcome in a defined population at a given point in time.
11. **Risk:** It is the probability of harm to be caused by the drug; it is usually represented in terms of Percentage or Ratio.

12. Signal: It is a new safety finding within safety data that requires further investigation. The signal can be *Confirmed, Refuted* or *Unconfirmed.*

HISTORY

The history of Pharmacovigilance started with the 1961 Thalidomide tragedy, W. McBride, an Australian doctor published a letter (case report) in the *Lancet* in December 1961, who first suspected a causal link between serious foetal deformities (*Phocomelia*) and Thalidomide, a drug used during pregnancy. Previously, Thalidomide was used as an antiemetic and sedative agent in pregnant women.[11]

In 1962, at the World Health Assembly a proposal was made that an international system for monitoring the adverse effects of medicines, based on reports from national agencies, should be established to prevent such a tragedy ever happening again. Then in 1963, at the 16th World Health Assembly, a resolution was adopted for a systematic collection of data and information on some serious adverse drug reactions after the drug was made available to the population.

In addition, in 1968 the WHO promoted the "*Programme for International Drug Monitoring*" with nearly 10 countries with only one agenda to develop a system that detects the previously unknown adverse effects of drugs. After that in 1971, an international database was established at WHO headquarters in Geneva.[12]

In 1978, this database was moved to Uppsala Monitoring Centre (UMC) at Uppsala Sweden and is managed by UMC. This database in now known as *VigiBase*. Its members submit the reports of suspected adverse reactions with drugs called as the Individual Case Safety Reports (ICSRs) to the *VigiBase*. The UMC has to review and analyse the data and share its conclusion to other member countries. As of now, more than 130 countries are full members of WHO programme and 30 countries are associate members.[13]

In recent years, Pharmacovigilance widened its range to Herbal medications, Traditional and Complimentary medications, Blood products, Medical devices and Vaccines. Substandard medicine, Medication errors, Lack of efficacy, Abuse of medicines are also included. In the mid-70s a French group of pharmacologists and toxicologists, the term Pharmacovigilance was proposed to define the activities promoting "*The assessment of the risks of side effects potentially associated with drug treatment*".[14]

AIM

The main Aim of Pharmacovigilance Programme is to ensure the safety of public for use of medicines. It helps to improve the safety in relation to use of medicines and medicinal products. It can detect any problem related to the use of medicines and can be used to communicate the findings to international level. It can be used for the assessment of benefit, harm and effectiveness of medicines, and used to encouraging a safe and effective use of medicinal products. Also, used to promote, educate and train people for better communication of pharmacovigilance in public.[15]

Need

Pharmacovigilance is needed to ensure the safety of medicines. In clinical trials prior to marketing of drugs, only a limited number of population is exposed to the effects and side effects of drugs. The information, which we collect during the Trials of a Drug, is incomplete regarding Adverse Reactions. There is a large variation in peoples around the globe, so a single drug can affect differently on different people.

Information regarding rare but serious adverse reaction, any chronic toxicity or drug interaction are often incomplete or not available. To promote the rationale use of medicines and to ensure public confidence. Lastly, due to Ethical reasons as not reporting an unknown serious adverse reaction is unethical for patients, healthcare professionals, manufacturers and proper authorities. As it is said "*To know of something that is harmful to another person who does not know, and not telling, is unethical".*[16]

Scope

The scope of pharmacovigilance is to monitoring continuously of any Adverse Drug Reactions. To reassess and update the *Benefit/Risk* ratio profile of any drug through the Periodic Safety Update Reports (PSURs).[17]

By evaluation the produced information, it can also be used for developing a risk evaluation and medication strategies, by a Black Box Warning method or by restricting the use and withdrawal of drug from market, in case if any ADRs are found. It is a continuous process of drug monitoring and drug surveillance, which can be done throughout the lifecycle of drug, so minimization in risk can be done.[18]

Adverse Drug Reactions (Adrs)

Adverse Drug Reaction is a response to a drug, which is noxious and unintended. It occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. (WHO, 1972). It is an unintended injury caused by taking medication. It may occur by takin a single dose of medication or by a prolonged use of medication and can also cause by combination of one or more drugs.[19]

An Adverse Drug Event (ADE) is a side effect, which occur with a drug, and its causal relationship with the drug is not known.[20]

Medication Error

It is defined as any type of error, which occurred in Prescribing, Dispensing and Administration of any kind of medicine, or drug, which may or may not lead to any serious adverse reaction. Any preventable event may lead to an inappropriate use of medication or cause any harm to the consumer. The main source of medication error is can be cause due to dispensing look alike medicine, can also be caused due to inadequate knowledge of medicine, dose miscalculation and errors in Labelling.[21]

Signal Detection

Signal is defined as "*Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously*". Usually, more than one report is required to generate a signal and depends on the severity of event and quality of information. It creates an alert that the drug may be associated with any unrecognized hazards. A Signal only provides a preliminary information and does not imply causation.

Various methods are for signal detection using spontaneous reporting. WHO-UMC uses the BCPNN (Bayesian Confidence Propagation Neural Network). Some other methods are MGPS (Multi item Gamma Poisson Shrinker), ROR (Reporting Odds Ratio), and PRR (Proportional Reporting Ratio).

Causality Assesment

Causality Assessment is a method used to evaluate a relationship between a drug exposure and the occurrence of the Adverse Drug Reactions. Clinician, pharmacists, pharmaceutical industry and healthcare professionals can do it.[22]

The most case reports in pharmacovigilance is suspected adverse reactions, and that is a major problem. Only few ADRs are certain or unlikely, rest are between possible and probable. Epidemiological studies (cohort studies) are needed to confirm it.[23] Many specific systems have been developed for solving these problems and for a harmonised and structures assessment of causality. None of the system give a reliable result.[24]

Advantages of Causality Assessment

- The disagreement between the assessors can be decreased.
- Relationship likelihood can be classified.
- Individual case reports can be marked.
- Scientific evaluation can be improved.

Disadvantages of Causality Assessment

- Accurate quantitative measurement of relationship likelihood cannot be given.
- It cannot distinguish a valid and invalid case.
- A connection between drug and event cannot be proved.
- The contribution of drug in any adverse event cannot be quantified.
- Any uncertainty cannot be changed to certainty.

WHO-UMC Causality Categories

Causality	Assessment
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable /Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that

	makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional /Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable /Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Source: Edwards IR, Biriell C. Harmonisation in Pharmacovigilance. Drug Safety 10(2): 93-102, 1994.

Naranjo Assessment

	Question	Yes	No	Do Not Know	Score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4.	Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	
7.	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	
	TOTAL SCORE				

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239245.

Scores

1. Definite ≥ 9
2. Probable (5-8)
3. Possible (1-4)
4. Unlikely (0)

Bayesian Odds Model

- Posterior odds = Prior odds × Likelihood ratio

Where,

- Posterior Odds = Overall Probability of AE due to drug,
- Prior Odds = Epidemiological & Clinical trial data,
- Likelihood ratio = Individual case report data (history, timing, severity, De-challenge etc.).

Pharmacovigilance Programme of India (Pvpi)

Government of India started the Pharmacovigilance Program of India in July 2010 at All India Institute of Medical Sciences (AIIMS), New Delhi. It was the National Coordinating Centre (NCC) for monitoring of adverse drug reactions until it shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad in April 2011.[25]

Scope and Objectives of PvPI

The objective of PvPI is to create a national system for the safety of patients and to analyse any new signals from reported cases. It analyses the *Benefit/Risk* ratio of marketed formulations, and generate evidence-based information on safety of medicines. The PvPI supports the regulatory authorities in decisions on use of medicines. In Pharmacovigilance activities, PvPI emerges as a national centre of excellence and can collaborate with other national centres for exchange of information and management of ADRs. It also acts as a training facility and consultancy to other national centres.[26]

National Coordination Centre

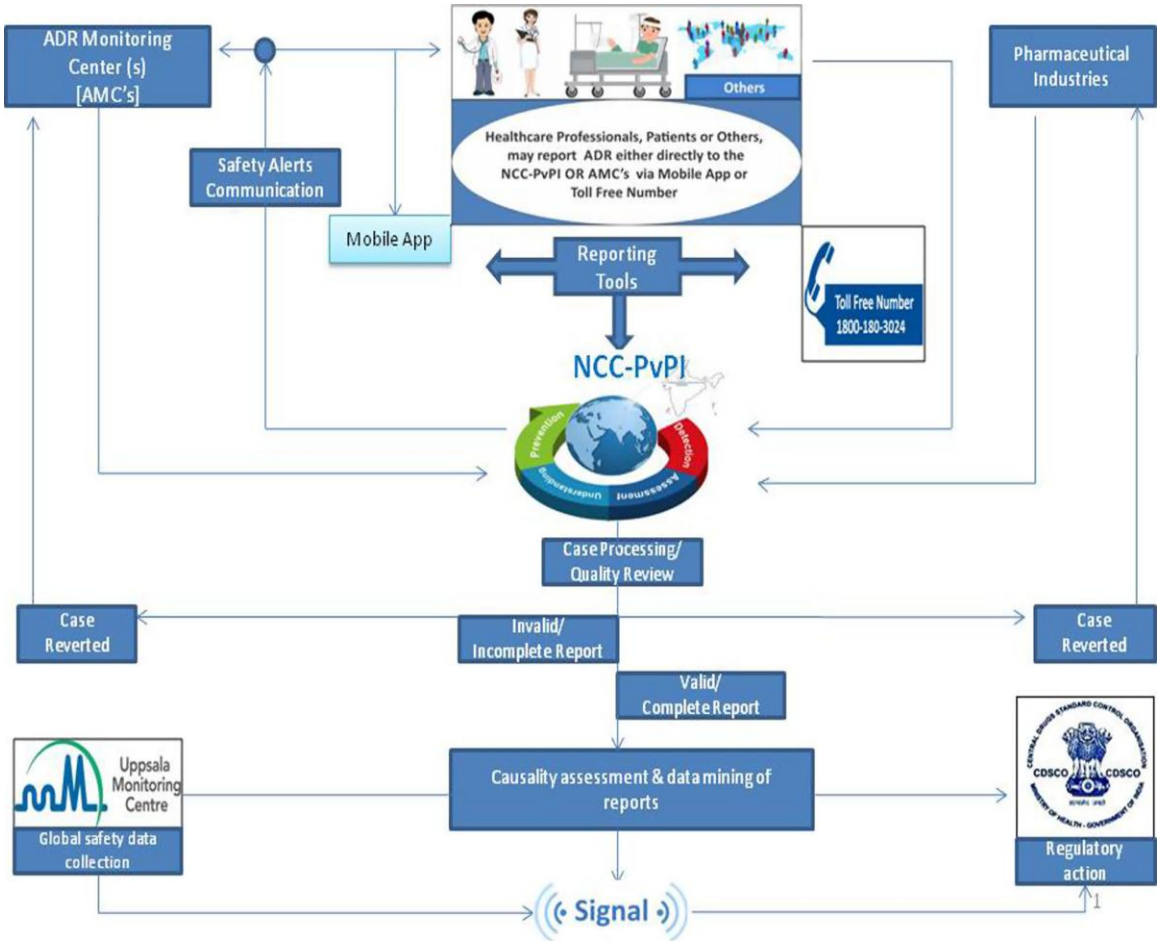
For the PvPI the Indian Pharmacopoeia Commission (IPC) functions as the National Coordination Centre and is an autonomous body under the Ministry of Health and Family Welfare, Government of India. It monitors all the adverse reactions of drugs in Indian Population and manage its own Pharmacovigilance database with respect to the use of medicines in India. NCC also participate in the WHO's International Drug Monitoring Programme and also Collaborated with UMC, Sweden.[27]

Adverse Drug Reactions Reporting in India

The monitoring of adverse drug reactions can be of two types: Active Surveillance and Passive Surveillance. In the Passive Surveillance no active measures are to be taken, reporting is entirely dependent on the reporter. Passive Surveillance includes Spontaneous

and Voluntary Reporting. Active Surveillance requires and Continuous Active follow up on Patients like Cohort Event Monitoring.

Flow of ADR Reporting in PvPI



Source: ***Image Copyright to Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission***[28]

Spontaneous Reporting

The Spontaneous report is an unsolicited report from a consumer or healthcare professional, any pharmaceutical company to the ADR Monitoring Centre (AMC) or NCC or Central Drug Standard Control Organisation (CDSCO) and it describes any unsuspected ADR in a patient by any medicinal product that does not have any data on the previous study.[29]

Suspected Adverse Drug Reaction Reporting Form

The NCC has designed a Form for recording of adverse reactions related to any medicine. Report describing the adverse reaction on individual patient of suspected ADR, which related to the administration of one or more medicinal products, is termed as ICSR.

All healthcare professional including clinician, dentists, pharmacists, nurses and non-healthcare professional like consumer, can report the ADR. Industries can also report through ICSR. Any adverse reactions related to pharmaceutical products, vaccines, traditional and herbal medicines, medicinal devices, and other pharmaceutical can also be considered. Reporting can be done by the use of Suspected Adverse Drug Reaction Reporting Form which is available on the websites of IPC and CDSCO. Reporting can also be done at AMCs by filling the suspected ADR form and submitted to associates at respective AMCs.[30]

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique

A. PATIENT INFORMATION

1.Patient Initials _____
2. Age at time of Event or date of birth _____
3. Sex ☐ M ☐ F
4. Weight ____Kgs

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

12. Relevant tests / laboratory data with dates

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction
☐ Death (dd/mm/yyyy)
☐ Life threatening
☐ Hospitalization/prolonged
☐ Disability
☐ Congenital-anomaly
☐ Required intervention to prevent permanent impairment / damage
☐ Other (specify)

15. Outcomes
☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered ☐ Other (specify)

C. SUSPECTED MEDICATION(S)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known))	Dose used	Route used	Frequency	Therapy dates (if known, give duration) Date started	Date stopped	Reason for use of prescribed for
i.										
ii.										
iii.										
iv.										

S.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. REPORTER (see confidentiality section on first page)

16. Name and Professional Address :_____
Pin code: _____E-mail _____
Tel. No. (with STD code): _____
Occupation _____Signature _____

17. Causality Assessment
18. Date of this report (dd/mm/yyyy)

Source: ***Image Copyright to Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission.***

WHO-UMC and PvPI

The NCC-PvPI collaborates to WHO-UMC for participating in the Programme for International Monitoring of Drugs, the UMC provide software for an effective communication between them.[31]

VigiFlow

It is an ICSR management system designed for the use at National Centres, and it is web-based. It has compliance with ICH E2B standards and a trademark of UMC. It is secure, fast and simple solution for ADR reporting. In VigiFlow, by the help of terminologies like WHO-DD, WHO-ART or MedDRA data can be entered manually. After the completion of report, the first version of ICSR is generated and automatically saved to VigiBase.

VigiBase

It is a WHO Global ICSR database, contains reports on adverse reactions from member countries. Its data resource is largest and most comprehensive. Easy retrieval and analysis of a data can be done, as it is a computerised system with recording of data in a structured and hierarchical manner.

VigiSearch

It is powerful search tool, which provide access to all the case reports in the VigiBase. It enables a comparison of national and international spontaneous adverse reactions, and can give access to ADR information on drugs.

VigiLyze

It is a powerful search and analysis tool, which provide information over all the ICSR reports present in VigiBase. It can compare national data to international data. Results are available in graphical and tabular formats.

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