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RESEARCH ARTICLE

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Comparitive Study of Pharmacovigilance System in India and USA

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ABSTRACT

A system of pharmacovigilance is a field of pharmacological sciences that deals with the Adverse Events Reaction reporting produced by medical devices and or drugs. One of the possible public health problems is an adverse event, which needs ongoing recording, assessment, and surveillance. Drug regulations have improved and got stronger since the 1937 sulphanilamide tragedy and the1960 thalidomide disaster. As such response, a Pharmacovigilance System was developed, which is capable of receiving, diagnosing, evaluating, monitoring, and mitigating harmful effects of medical products.

The Central Drug Standard Control Organization-CDSCO regulates India's pharmacovigilance system, whereas the United States Food and Drug Administration-USFDA regulates the US pharmacovigilance system. In India, the pharmacovigilance programme monitors adverse drug responses. India has a Pharmacovigilance Program in place to track adverse drug reactions. The United States likewise has strict laws in place to strengthen Food & Drug Administration (FDA) pharmacovigilance requirements. (WHO) -World Health Organization established an International Monitoring System in collaboration with (UMC) Uppsala Monitoring Centre.

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INTRODUCTION

World Health Organization defines pharmacovigilance (PV) as "the pharmaceutical science concerned to the branch of pharmacy dealing with the detection, diagnosis, understanding, and mitigation of adverse drug reactions (ADRs), particularly long-term and short-term reactions." PV has a variety of tasks, including identifying, quantifying, and documenting drug-related issues that cause drug-related injuries. These adverse drug reactions not only make patient's life more difficult, but they also increase morbidity and death, putting a costly strain on society. PV was originally noted in a letter sent by Dr. William McBride and released through the Lancet in December 1961. [1]

KEYWORDS:
Adverse drug reactions, Uppsala monitoring centre (UMC), Pharmacovigilance programme of India, Med watch, National Coordination Centre .

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Etymological origin

Pharmacovigilance: Pharmakon = drug in Greek language, Vigilare = to keep watch in Latin.
As a result, Pharmacovigilance is a critical post-marketing technique for safeguarding the safety of pharmaceuticals and other health-related goods. Other than drug regulatory authorities in India namely the Central Drug Standard Control Organization (CDSCO) and within United States, the United States Food and Drug Administration (USFDA), the International Conference on Harmonization Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, Pharmacovigilance Planning and the Uppsala Monitoring Centre of World Health Organization(WHO-UMC) also support the development, enrichment, and surveillance of pharmacovigilance systems worldwide .[2]

Chronological Development of PV

1747: James Ling rumoured run showing effectiveness of juice in interference of scurvy.

1937: Sulphanilamide disaster, wherever sulphonamide was dissolved in diethyleneglycol resulting in death of quite 100 folks because of nephritis.

1938: The presymptomatic toxicity and pre-marketing clinical studies created obligatory by government agency.

1950s: anaemia caused thanks to use of Chloromycetin.

1960: The government agency started hospital primarily based drug computer programme.

1961: sedative-hypnotic disaster.

1963: sixteenth world health assembly recognized importance to speedy action on ADR.

1968: institution of International Drug computer programme by UN agency.

1970s: Clioquinol was found to be coupled with Sub-acute myelo-optic pathology.

1980s and 1990s: several medicines with serious adverse effects were recorded.

1996: India started world commonplace run.

1997: India has enrolled in the ADR computer programme.

1998: Pharmacovigilance activity phase started in India.

2002: 67th Indian National Pharmacovigilance Centre is established.

2005: systematic clinical trials were conducted in India.

2009-2010: PV set up of India was initiated and enforced.[3]

METHODOLOGY

Pharmacovigilance System in India

History

India proposed the Adverse Drug Reaction Monitoring System in 1986. (ADR monitoring System). There were 12 regional centres.

In 1998, India became a member at the World Health Organization's ADR Monitoring Program.

India launched its National Pharmacovigilance Program in 2004-08, which was divided into two zonal, five regional, and 24 peripheral regions. [4]

PvPI: PharmacovigilanceProgrammein India

It has a five-year strategy with five phases: beginning with initial phase (2010-11), (2011-12) -expansion and consolidation, (2012-13)-expansion and maintenance, (2013-14) - expansion and optimization, then finally Excellence Phase (2014-15).

The Government of India's primary drug safety monitoring initiative, the (PvPI) Pharmacovigilance Programme of India, collects and analyses drug-related adverse events. Because adverse medication reactions are still one of the primary of morbidity and mortality globally, it is critical to keep track of them. Ministry of Health and Family Welfare (MoHFW) of India's Government inaugurated the Pharmacovigilance Programme of India (PvPI) in July 2010, with the All India Institute of Medical Sciences (AIIMS) in New Delhi serving as the National Coordination Centre (NCC).[4] Communication of data flow and process flow of PvPI is given in Figure 1and Figure 2.

AIMS AND OBJECTIVES

- Produce a Nation-wide system for patient-safety by guaranteeing drug-safety.
- Establish and analyse new signals from the rumoured cases.
- Analyse the benefit-risk quantitative relation of marketed medications.
- Generate evidence-based info on safety of medicines.
- Support regulative agencies within. the decision-making method on use of medicines.
- Communicate safety info on use of medicines to varied stakeholders for preventing/ minimi-zing the danger.
- Emerge as a National Centre of Excellence for Pharmacovigilance Activities.
- Collaborate with different National Centres for exchange of knowledge and data management.
- Offer coaching and practice support to different National Pharmacovigilance Centres across the world.
- Promote rational use of medicines.[5]

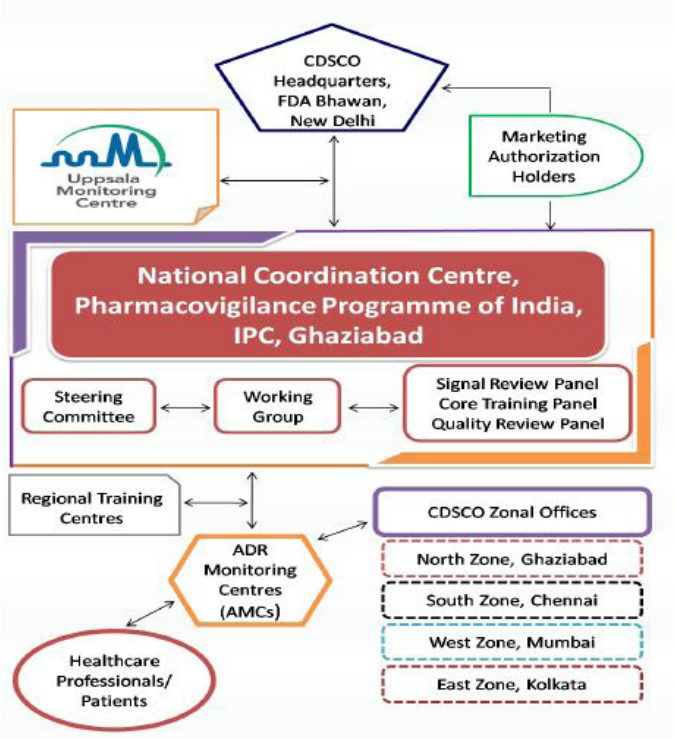


Fig. 1: Communication of data flow in PvPI

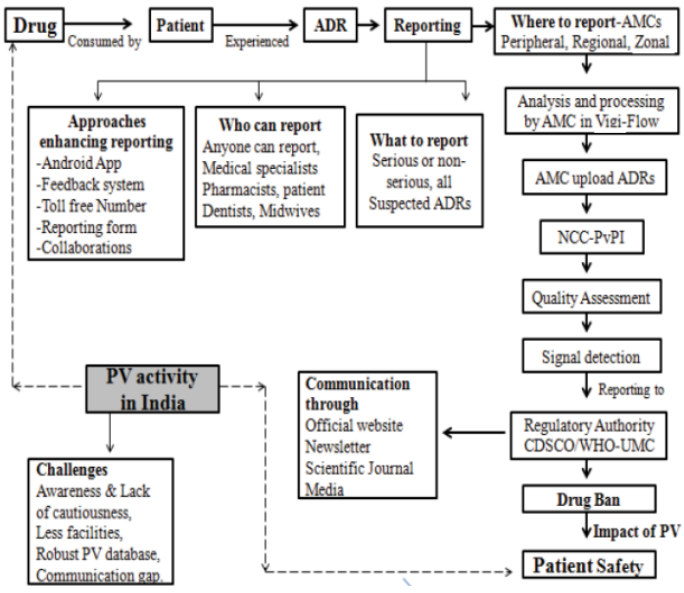


Figure. 2: Process Flow PV in India

PROCEDURE OF ADR REPORTING IN INDIA

ADR reporting in India under PvPI is mainly done through 3 ways

1. Healthcare Professional
2. Consumer Reporting
3. Public Health Programme-PHP

Processing of ADR

At the AMCs, all ADR reports from various sources are gathered. AMC PV employees research, validate, and prioritise the report, as well as execute a tentative causality evaluation. The ADR forms that have been examined are then sent to an authorised coordination centre for further processing. The AMC personnel keep track of all of the centre's operations and perform ADR monitoring of medications according to the standard watch list. After that, the coordinating centres undertake a final causation assessment and enter the results into the PV database. These centres additionally create and transmit to WHO-UMC an aggregate report of ADRs gathered at the specified time period. The results of the PV analysis are then incorporated into a larger community health programme. Data for ADR Reporting Criteria has been given in TABLE 1.

Finally, the combined ADR data is uploaded to the UMC database via the Vigi-Flow database. The UMC team analyses the data and discovers a drug-ADR association, referred to as a signal, which is a critical component, and communicates with NCC-PvPI via CDSCO to suspend the marketing or usage of the medicine in India.[2]

1. Health-care professional is required to keep track of adverse occurrences (Doctors including Dentists Nurses and Pharmacists)
2. ADR filing form was sent to AMC (ADR Monitoring Centre) or the NCC (National Coordination Centre). Verify for completion of essential fields and examine in reports for central evaluation to NCC conducted by AMC after entering of ADR information in vigiflow.
3. Following submission of the application with report for central evaluation, prepare the report in vigiflow on every ADR entry and archive the electronic copy. Take notice of the auto-generated Global UNIQUE NUMBER in the logo notebook for each vigiflow entries.
4. Every report is checked for consistency and authenticity by AMC personnel. Casualty evaluation is done by the Centre coordinator's Deputy Supervisors. Technical colleagues register ADR cases in the vigi flow according to WHO-UMC guidelines
5. Personnel from the AMC NCC follow up to ensure that the form as well as impact evaluation of the case are appropriate. Vigiflow receives follow-up data as well. The original paper records of ADR forms submitted in vigiflow would be maintained in a secured cabinet with

Table 1: ADR Reporting Criteria

What to report	*When to report?*	*Who to report*	*How to report*	*Where to report*
- Death/Life-threatening - Hospitalization - Congenital anomaly – Medically significant - Lack of efficacy - All serious or non serious reactions	• Within 30days in Non serious cases • within 7 days in all death event or serious cases whenever possible	Physicians Medical specialists Dentists Pharmacists	ADR reporting form - Toll free number: 1801803024 E-mail: pvpi@ipcindia.net	To Nearest AMC -Like Various Zonal offices: West Mumbai, South Chennai, East Kolkata, , North Ghaziabad, or directly to CDSCO/WHO

Table 2: Comparative Study Of Pharmacovigilance Regulation In India&Usa

PARAMETERS	*INDIA*	*USA*
• Regulatory	• CDSCO	• FDCA and FDA
• Authority	• National Co- ordination centre	• CDER and CBER
• Pharmacovigilance Responsible Authority	• ADR and PSUR reporting Follow PvPI	• Good Pharmacovigilence Practices & Guidance for Industry Pharmaco-epidemiologic Assessment
• Guidelines	• ADR information is given by PvPI	• Post-market reporting of possible adverse events is covered under Sec. 314.80.
• Adverse Drug Reaction	• National Authorization Process	
• Process for Pharmacovigilance Filling	• No specific Module is available	• FDA Adverse Event Reporting System (FAERS)
•	• For reporting all products only one ADR form is available	• No specific module is available
• Quality and Pharmacovigilance system	• ICH E2C format is required	1. Voluntary reporting for Healthcare professionals and consumers through ADR form 3500B
• Forms		2. ADR form 3500A is required for mandatory reporting of regulated industries and facility customers.
• Periodic Safety Update Report-PSUR		• ICH E2C format is required

only the coordinator, technical associates and also sub coordinator having access.

6. The ADR form can indeed be scanned then archived as an electronic copy. All ADRs should be sent to NCC through a COPY.
7. Under the present scope of the PvPI, consumers' spontaneous reports may not be deemed acceptable ADRs. When a client reports an ADR, AMC staff makes every effort to approach the patient's health care practitioner to clinically verify the ADR and acquire enough information about it. The AMC will keep track of every effort at follow-up.
8. ADRs can be reported in the Public health programmes. Any health care practitioner involved in a public health initiative can report ADR to the nearest AMC. It should also be reported in vigiflow with a report heading that starts with PHP. [2] [3]

CHANNELS FOR REPORTING AE/ADR IN INDIA

1. Form of Suspected ADR Reporting to Healthcare Professionals (HCPs)

Suspected ADR Reporting Form was created for healthcare providers to record thorough information concerning an adverse event or reaction. This form is available on IPC website (www.ipc.gov.in) or CDSCO website (www.cdsco.gov.in) and in National Formulary of India 2016

2. Medicines Side-Effects Reporting Form (Consumers)

Consumers/patients may also make use of Medicines Side-effect Reporting Form for reporting any suspected AE/ ADR to PvPI. This form is available within 10 Indian languages: Hindi, Kannada Bengali, Malayalam, Marathi, Gujarati, Oriya, Assamese, Telugu and Tamil [4]

3. Form for Suspected ADR Reporting (For drugs used in Prophylaxis/ Treatment of COVID-19)

The Form of Suspected ADR Reporting is designed for Healthcare professionals during pandemic to capture detailed information about an AE/ADR related to the drugs used in Prophylaxis/ Treatment of COVID-19. This form is available on IPC (www.ipc.gov.in) [4]

4. Personal Protective Equipment (PPE) Adverse Event Reporting Form

In view of COVID-19 Pandemic, NCC-MvPI has specially designed a PPE Adverse Event Reporting Form, It principally intends to gather the adverse events (AEs) connected with the use of personal protective equipment (PPE) for medical purposes.

5. Miscellaneous ADR Reporting Forms

Healthcare Professionals and other stakeholders can also report AEs/ADRs using specific forms designed purposely for reporting AE/ADR associated with Medicines used in Kala-azar treatment .

6. PvPI Helpline

Patients/ Consumers/ HCPs may report or submit any suspected ADRs connected through the use of medicinal/ herbal products/ vaccines or medical devices to NCC-PvPIvia Toll-Free Helpline No. 1800-180-3024. [5]

Table 3: Further Comparision Of Pharmacovigilance In India&Usa

PARAMETERS	*INDIA*	*USA*
• Pharmacovigilance System Master File-PSMF	• Not Required	• Not Mentioned
• Pharmacovigilance Inspection	• Not Mentioned	• Mentioned in Post-marketing Adverse Drug Experience (PADE) Reporting Inspection.
• Pharmacovigilance	• Not Mentioned	• -----
• Audit		
• Risk management System	• Risk Management System is given in PvPI	• Risk Management System is given in Risk Management Guidance under Guidance for Industry, Good Pharmacovigilance Practice and Pharmacoepidemiologic assessment.
• Database	• Vigiflow software	• FEARS for small database and Sentinel System for Large database
• Data Lock Point for PSUR	• 60 days	• 70/90 days
• Safety Communication	• Not mentioned	• E2E Pharmacovigilance Planning is included in the Guidance for Industry.
• Risk Minimization Measure	• Not mentioned	• Risk Minimization Action Plans-Risk MAP recommendations are used to reduce risk.
• Non Serious ADR reporting time period	• Not required on serious basis	• ---
• Serious ADR reporting time period	• Within 15 days	• Within 15 days.

PHARMACOVIGILANCE IN UNITED STATES

In the United States, there are two forms of ADR reporting: external and internal. ADR reporting to third parties might be optional or mandated. There are a number of important national voluntary reporting systems. [6]

History:

Following the Elixir Tragedy in 1937 and the Thalidomide Tragedy in 1960, Food & Drug Administration (FDA) amended its regulations to require drug manufacturers to show the safety and efficacy of their products before receiving marketing approval. [6]

Regulations:

Health and Human Services - United States of Food and Drug Administration (FDA) of America regulates the Centre for Drug Evaluation and Research (CDER) and Centre for Biologics Evaluation and Research (CBER) which aids in pharmacovigilance

PROCEDURE FOR REPORTING ADR IN THE UNITED STATES

Adverse drug reactions are reported by 21 CFR 314.80 to the FDA, Post-Marketing Reporting of ADRs, in the United States, and the reports are sent to the (FEARS) FDA Adverse Event Reporting System by the FDA. [7]

- ADR is reported using the technique outlined through following processes.

1. Health care professionals (Nurses, Physicians, Pharmacists& Others) and consumers (Family members, Patients, Lawyers and other) each submit two copies of their post-marketing ADR data to the FDA.
2. ADRs are reported to the FDA through Med Watch, and each report is issued a distinctive Code number that is not more than eight characters long and given below are their form numbers.
    - FDA 3500BForm: Healthcare Professionals and Consumers Voluntary reporting.
    - FDA 350**0AForm :** Mandatory reporting of User Facilities and Regulated Industries.
3. The FDA's Adverse Event Reporting System, (FEARS) receives reports. Clinical reviewers at the CDER and CBER evaluate reports. Center for drug evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).
4. If a possible safety problem is detected in FAERS, further investigation is carried out, which may involve performing investigations. Using other huge databases, counting raw data, and any correspondence linked to adverse drug experiences that the applicant is aware.
5. FDA may revoke an applicant's approval and, as a result, prohibit continuing commercialization of the pharmaceutical product that would be the matter of that proposal, if the candidate fails to keep and maintain records and file reports as required by this section. [7]

CHANNELS FOR REPORTING ADES IN US

1. Reporting through Med Watch

ADEs can always be submitted to the FDA officially through Med Watch by a healthcare professional or a patient, or they can report to the manufacturer, who then reports them to the FDA.

2. Reporting Directly to the FDA

There are three options for submitting a voluntary report:

1) Complete Form 3500 online at www.accessdata.fda.gov/scripts/medwatch;
2) For reporting through telephone Call 1-800-FDA-1088 to; and
3) Download a copy of Form 3500 at (www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf) and either fax it to (1-800-FDA-0178) or mail it back (Med Watch, 5600 Fishers Lane, Rockville, MD 20852-9787) using the postage-paid addressed form. This may be most appropriate where there are attachments to submit with the report.

3. Reporting to the FDA via the Manufacturer

The most of ADEs are notified to the drug's manufacturer, whose contact details may be found on the company's website. The manufacturer is responsible for collecting any important details from the reporter then communicates it to the FDA. The maker must report ADEs that are serious and unanticipated to the FDA within 15 days of receiving the information. All ADEs are also submitted to regulatory bodies on the routine basis by the manufacturer through periodic safety reports. These reports cover patient exposure (both post marketing and clinical trial), presentation of case summaries, research data, and overall safety review and comprise summaries of all ADE reports in a certain time period. [8]

ICSR SAFETY REPORTING REQUIREMENTS

After any new drug application - (NDA), abbreviated new drug application- (ANDA), or biologic licence application - (BLA) is authorised, irrespective of whether a pharmaceutical product is marketed, all ADEs from all sources are to be reported for FDA by the permit holder. The FDA Adverse Event Reporting System (FAERS) is a network that keeps track of all reports of adverse reactions. Containing information on pregnancy, abuse, misuse, prescription abuse errors, and quality concerns. This database is used by the FDA to track and supervise pharmaceuticals after they have been authorised. Both the CDER and the CBER examine the software›s safety data to ensure whether human-use medications maintain safe and efficacious. Any possible safety signs discovered are further explored. The regulatory rules for reporting major ICSRs in a hurry are similar to those for other ICH zones. which demand reports within 15 days. The Electronic Submission Gateway should be used to submit ICSRs electronically. [9] [10]

PHARMACOVIGILANCE AND WORLD HEALTH ORGANIZATION-WHO

Upon the thalidomide disaster in 1961, WHO Collaborating Centre of International Drug Monitoring partnered with WHO

to create the International Drug Monitoring Program, and WHO promoted Pharmacovigilance- PV at the country level. As of the end of 2010, 134 nations were participating in the WHO-PV Programme. WHO Programme for the International Drug Monitoring is in charge of UMC which manages the developing universal pharmacovigilance system, which already encompasses more than 130 countries. The WHO Collaborating Centre follows WHO guidelines and collaborates closely with the WHO's headquarters. In terms of organisation and staff, UMC is distinct from WHO.[11] [12]

COLLABORATION BETWEEN PVPI AND WHO-UMC

To be able to take part in a programme of international drug monitoring, NCC- PvPI collaborates with WHO-UMC. The following software tools are provided by WHO-UMC which is working to make the PvPI goals more efficient. [13]

1. VIGIFLOW

Vigiflow is web-based ICSR control system created specifically for national centres participating in the WHO's International Drug Monitoring Program.

2. VIGIBASE

Vigibase is the WHO global ICSR database. Since 1968, it has collected reports of adverse responses from member nations. [13]

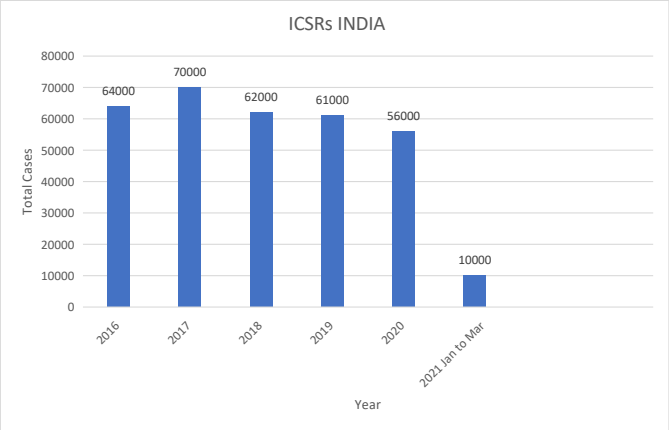
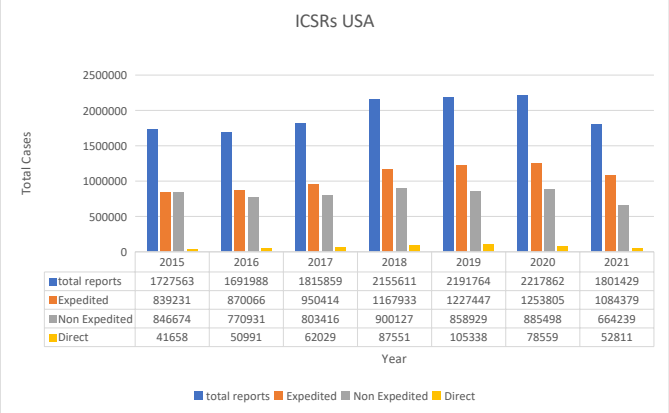


Fig. 3: Data of ICSR -INDIA



	2015	2016	2017	2018	2019	2020	2021
total reports	1727563	1691988	1815859	2155611	2191764	2217862	1801429
Expedited	839231	870066	950414	1167933	1227447	1253805	1084379
Non Expedited	846674	770931	803416	900127	858929	885498	664239
Direct	41658	50991	62029	87551	105338	78559	52811

Fig. 4: Data of ICSR - USA

3. VIGIMINE

VigiMine gives access to statistical data on all drug- ADR pairs reported toVigibase and was launched in 2008 as a new development in Vigisearch.

4. VIGIMED

VigiMed is a part of UMC collaboration portal, a web -based platform managed by the UMC.

5. VIGISEARCH

Vigisearch is powerful search tool that provides access to all case reports in vigibase.

6.VIGILYSE

Vigilyse is a powerful search and analysis tool that provides access to more than 8 million ICSRs in Vigibase, submitted from over 100 countries [13]

WHO-UMC CAUSALITY ASSESSMENT SYSTEM

WHO-UMC system was created in collaboration with National Centres partaking in the Mission for the International Drug Monitoring and is intended to be a useful tool for evaluating case reports. It is essentially a combination evaluation that considers the clinical-pharmacological components of such case history as well as the quality of the observation record. Because pharmacovigilance is primarily concerned about detecting unknown and unpredictable adverse effects, other factors like prior information and statistical chance play a smaller role in the system. Because of the definitions' semantics, individual assessments may differ, which is acknowledged. Other algorithms are either too sophisticated or too particular to be useful in general. This technique directs the broad justifications that should be used to pick one category over another [14] [15]

RESULTS

Comparative study of Pharmacovigilance system Regulation between INDIA and USA is given in the TABLE.2,3 and the trend analysis data for Individual case study reports (ICSR) is given in India (Figure.3) [17]and USA (Figure.4). [18]

DISCUSSIONS AND FUTURE PROSPECTIVE

Pharmacovigilance (PV) is an important aspect of drug regulation. PV plays a critical role in detecting, assessing, and disseminating adverse drug reactions through a variety of methodologies. ADRs cause significant damage to patients and can possibly result in morbidity and death. PV databases aid in the promotion of safe drug use and the safeguarding of public health. The systems of PV in United States and India are compared in this article. Because of technology advancements, the United States have well-established PV systems

India is the world's largest pharmaceutical production and a key clinical research centre, necessitating a more demanding PV setup. Furthermore, these systems follow a consistent

framework that includes post marketing surveillance, risk management, post-approval research, and enforcement, all of which are dependent on a regulatory authority. [16]

CONCLUSION

This article provides a quick summary of the Pharmacovigilance system for reporting Adverse Drug Reactions in India as well as United States. Pharmacovigilance is the only way to ensure the safety of the drug throughout the life cycle. It is very much crucial as the clinical trials have limitation to detect the rare and very rare ADRs. India has launched a five-phased pharmacovigilance programme in partnership with WHO-UMC. The pharmacovigilance system in India is still in its early stages. It only allows for drug-related adverse reactions to be reported. This will aid in the creation of a vast database of ADRs. United States has well-developed and stronger pharmacovigilance rules. For applicants who want to report Adverse Drug Reactions, they have two separate ADR reporting mechanisms. There are significant effects on the pharmacovigilance to make it more functional after the concept has emerged and day by day, we are getting closer to the destiny. It is our responsibility to ensure well-functioning of pharmacovigilance system. ADR reporting should be taken as a very important duty not as an extra clinical burden by health care professionals to ensure using of safer drugs.

Ethical Approval

This study and research has been done using only online public available data, documents and records in India and USA. There is no involvement of specific individual Animal or Human participants. So, this article does not require Ethical Approval.

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Conflicts of Interest: No conflicts of interests.

Informed Consent: As the research study did not include any human participants. So, the informed consent is not been required to be taken.

Authorship Contributions: Only corresponding Author contributed for this research study.

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