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A COMPARATIVE STUDY OF REGULATORY ISSUES ON PHARMACOVIGILANCE IN US, EUROPE AND IN INDIA: A REVIEW

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ABSTRACT

The primary focus of the pharmacovigilance (PV) practice has been on the collection, assessment, and reporting of the adverse drug reactions to medicinal products. Globalization of the pharmaceutical industry has prompted efforts to toward harmonization of PV practices worldwide to enable improved knowledge of medicine's benefit-risk profile and risk communication. Even as PV has evolved over the past decade, there still exist few areas of discordance across global PV practices. This article compares the PV legislation in the US, EUROPE and INDIA with a view to understand areas of harmony in the current legislation across regions. Work helps to design solutions and strategies toward creation of a comprehensive PV system, which can be easily implemented across the globe, thus promoting the safer use of medicines.

KEYWORDS: Adverse drug reaction, drug safety, pharmacovigilance.

INTRODUCTION

- The pharmacological science relating to the *collection, detection, assessment, monitoring, and prevention* of adverse effects with pharmaceutical products.
- As such, pharmacovigilance heavily focuses on adverse drug reactions, or ADRs, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy.

- The condition that this definition only applies with the doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological disorder function was excluded with the latest amendment of the applicable legislation.
- Medication errors such as overdose, and misuse and abuse of a drug as well as drug exposure during pregnancy and breastfeeding, are also of interest, even without an adverse event, because they may result in an adverse drug reaction.
- Information received from patients and healthcare providers via pharmacovigilance agreements (PVAs), as well as other sources such as the medical literature, plays a critical role in providing the data necessary for pharmacovigilance to take place.
- In fact, in order to market or to test a pharmaceutical product in most countries, adverse event data received by the license holder (usually a pharmaceutical company) must be submitted to the local drug regulatory authority.
- Ultimately, pharmacovigilance is concerned with identifying the hazards associated with pharmaceutical products and with minimizing the risk of any harm that may come to patients. Companies must conduct a comprehensive drug safety and pharmacovigilance audit to assess their compliance with worldwide laws, regulations, and guidance.

USFDA

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components) and also the following.

- ✓ *Safety signal identification,*
- ✓ *Pharmacoepidemiologic assessment and safety signal interpretation, and*
- ✓ *Pharmacovigilance plan development.*

EMA

- ✓ Good pharmacovigilance practices (GVP) for the European Union A set of guidelines for the conduct of pharmacovigilance in the EU, drawn up based on Article 108a of Directive 2001/83/EC, by the European Medicines Agency in cooperation with competent authorities in Member States and interested parties, and applying to marketing authorisation holders in the EU, the Agency and competent authorities in Member States.

INDIA

- ✓ Pharmacovigilance in India was initiated way back in 1986 with a formal adverse drug reaction (ADR) monitoring system, under supervision of the drug controller of India. ...

Later, the National Programme of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programme of India (PvPI) in 2010.

AIM

Aim is to collect information regarding:

Pharmacovigilance guidelines in US , Europe and in India by comparing them and also how the countries are initiating patient safety through the detection, assessment, understanding and prevention of adverse effects and other drug related problems.

METHODOLOGY

Pharmacovigilance- India

- **History**

In 1986, India proposed Adverse Drug Reaction Monitoring System (ADR monitoring System). It had 12 regional centers. India joined World Health Organization-WHO-ADR Monitoring Programme in1998. In 2004-08, India had started National Pharmacovigilance Programme which was performing under 2 Zonal, 5 regional and 24 Peripheral Regions. Currently India is having Pharmacovigilance Programme of India which has commenced from 2010.

- **Pharmacovigilance programme of india (Pvpi)**

It is 5 year programmed and it comprises of 5 phases:- Initial Phase (2010-11), Expansion and Consolidation phase (2011-12), Expansion and maintenance phase (2012-13), Expansion and optimization phase (2013-14). The Excellence Phase (2014-15). Due to considerable social and economic consequences of adverse drug reactions there is a need to engage health-care professionals and the public at huge, in a well-structured programme to build collaborations for monitoring adverse drug reactions. The purpose of the programme is to assemble data, examine it and use the inferences to recommend informed regulatory interventions, besides interconnecting risks to healthcare professionals and the public.

The Pharmacovigilance Programme has the following signposts:

- ✓ To nurture a culture of notification, To engross several healthcare professionals and NGOs in the drug monitoring and information distribution processes,
- ✓ To achieve such operational efficiencies that would make Indian Pharmacovigilance Programme a benchmark for global drug monitoring endeavors.

➢ **Regulations**

- The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in partnership with Indian Pharmacopeia commission, Ghaziabad has initiated a nation-wide Pharmacovigilance Programme for protecting the health of the patients by guaranteeing drug safety.
- The Programme is being coordinated by the Indian Pharmacopeia commission, Ghaziabad works as a National Coordinating Centre (NCC).
- The centre operates under the supervision of a Steering Committee.The programme is coordinated by the National Pharmacovigilance Centre (NPC) at CDSCO.
- The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee (NPAC) to recommend procedures and guidelines for regulatory interventions.
- The Pharmacovigilance programme of India encourages reporting all the suspected adverse reaction related to drug which also includes of those suspected to have been caused by herbal, traditional or alternative remedies.

➢ **ADR Reporting procedure of india**

In India Reporting of ADR is done through following three ways under PvPI:

✓ 1. Healthcare Professional

✓ 2. Consumer Reporting

✓ 3. Public Health Programme-PHP

The reports are recorded through ADR reporting form by ADR monitoring center /National Co-ordination Centre. Then they are entered into the vigiflow software and reports re-checked for it completeness.

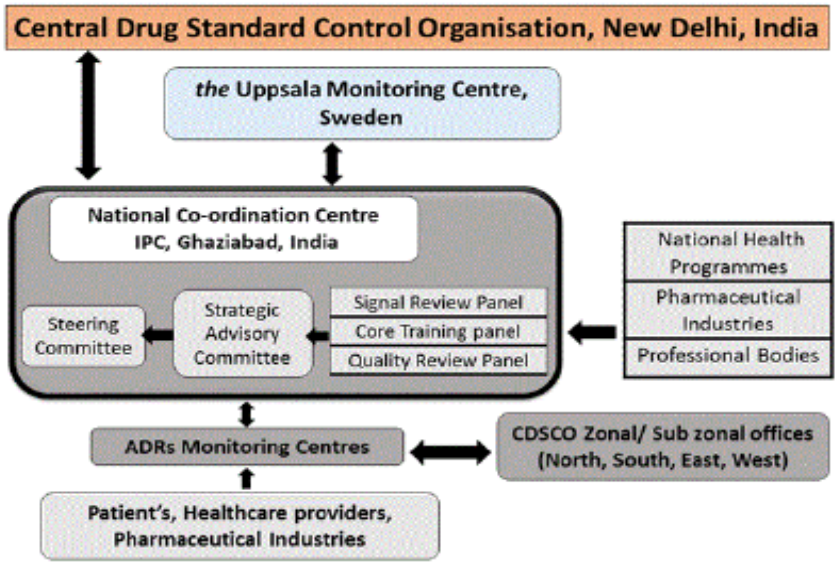


Figure 1: Flow of ADR reports in the indian pharmacovigilance system.

Pharmacovigilance- USA

➢ **History**

After the Elixir Tragedy in 1937 and The Thalidomide Tragedy in1960 United States have revised the Food and Drug Administration Regulations to demonstrate the safety and efficacy of drug before issuing marketing authorization.

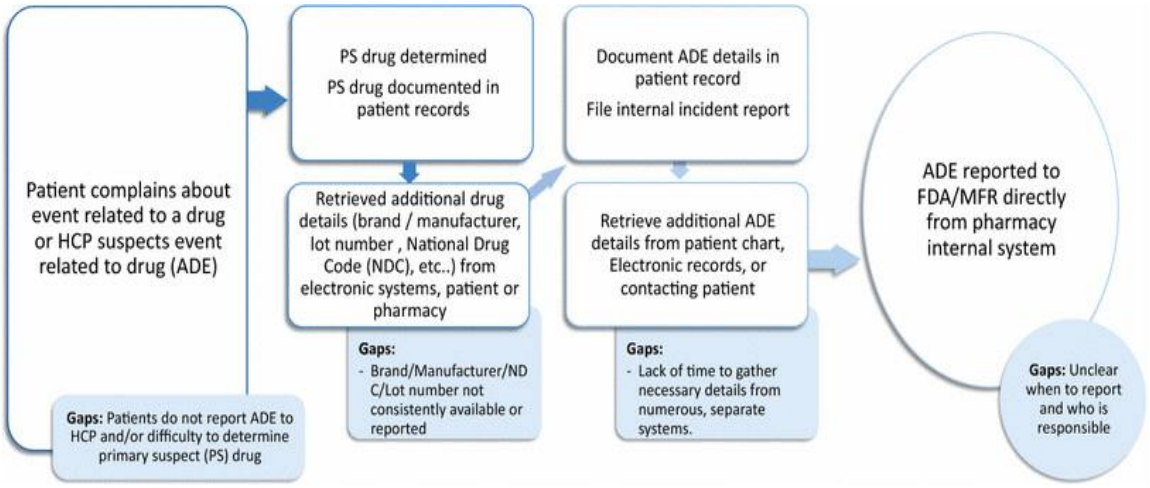
➢ **Regulations**

U.S. Department of Health and Human Services and Food and Drug Administration – FDA regulates pharmacovigilance with help of Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

➢ **ADR Reporting procedure of USA**

- In USA, Adverse Drug Reactions are reported according to the Post Marketing Reporting of ADRs 21 CFR 314.80 to US Food and Drug Administration and FDA submit the Reports to the FDA Adverse Event Reporting System-FEARS.
- Healthcare Professionals (Physicians, Pharmacists, Nurses and Others), Consumers (Patients, Family Members, Lawyers and Other), Regulated industries, Facility Users will report ADR.

- Healthcare professionals, consumers, Regulated Industry and User facilities record the ADRs through either ADR form 3500A or ADR form 3500B and send these reports to FDA.



Eudra vigilance (European union drug regulating authorities pharmacovigilance)

➢ **History**

- The EU5 (France, Germany, Italy, Spain, United Kingdom) accrued ~17% of global 2011 pharmaceutical expenditures.
- PV efforts in the EU are coordinated by the European Medicines Agency (EMA) and are conducted by the national competent authorities (NCAs).
- The main responsibility of the EMA is to maintain and develop the pharmacovigilance database consisting of all suspected serious adverse reactions to medicines observed in the European Community; the data processing network and management system is called EudraVigilance and contains separate but similar databases of human and veterinary reactions.

➢ **Regulations**

- Article 28e of Regulation (EC) No 726/2004 specifies that "the Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorization, including the use of collaborative approaches, to maximize use of resources available in the Union.“

- The establishment of a functioning EMA pharmacovigilance system is to be the subject of regular audits and regular publication of a report by the European Article 87a(b) of

Regulation (EC) No 726/2004 sets the framework for Commission Implementing Regulation (EU) No 520/2012 by stating that "[i]n order to harmonize the performance of the pharmacovigilance activities provided for in this Regulation.

- Commission, as outlined in Articles 28f and 29 of Regulation (EC) No 726/2004.

- **ADR reporting procedure of EU**

EudraVigilance Clinical Trials module: suspected unexpected serious adverse reactions (SUSARs) reported by sponsors of interventional clinical trials;

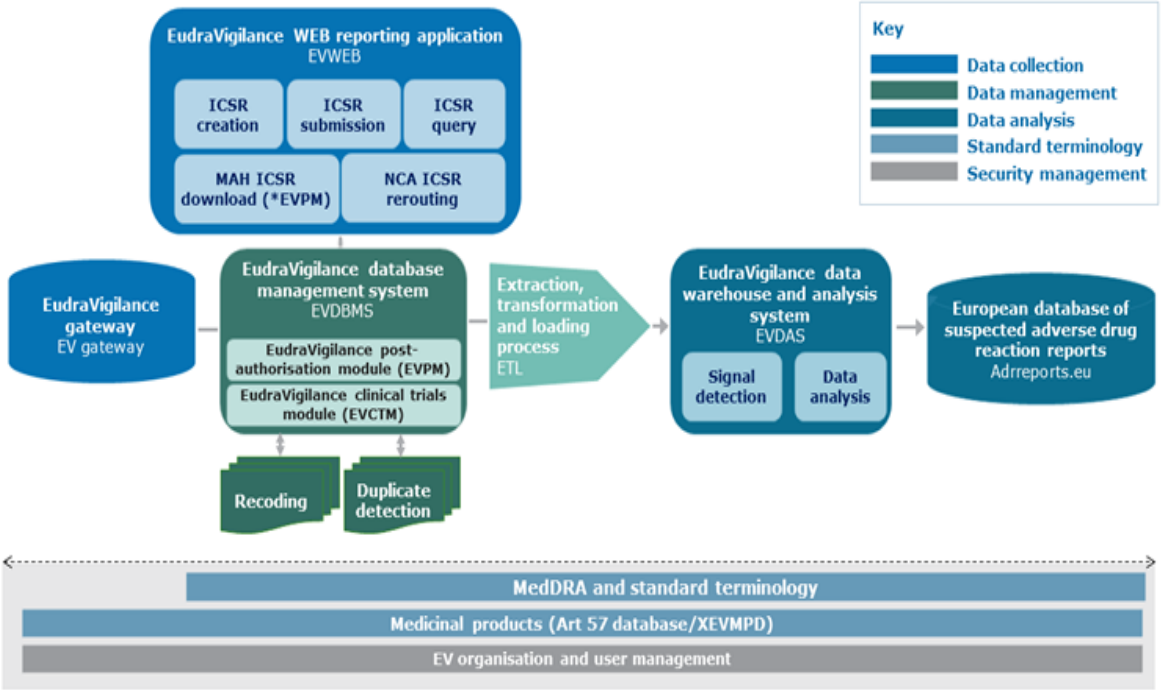
EudraVigilance Post-authorisation module: Suspected serious and non-serious side effects from: Healthcare professionals' and patients' spontaneous reporting;

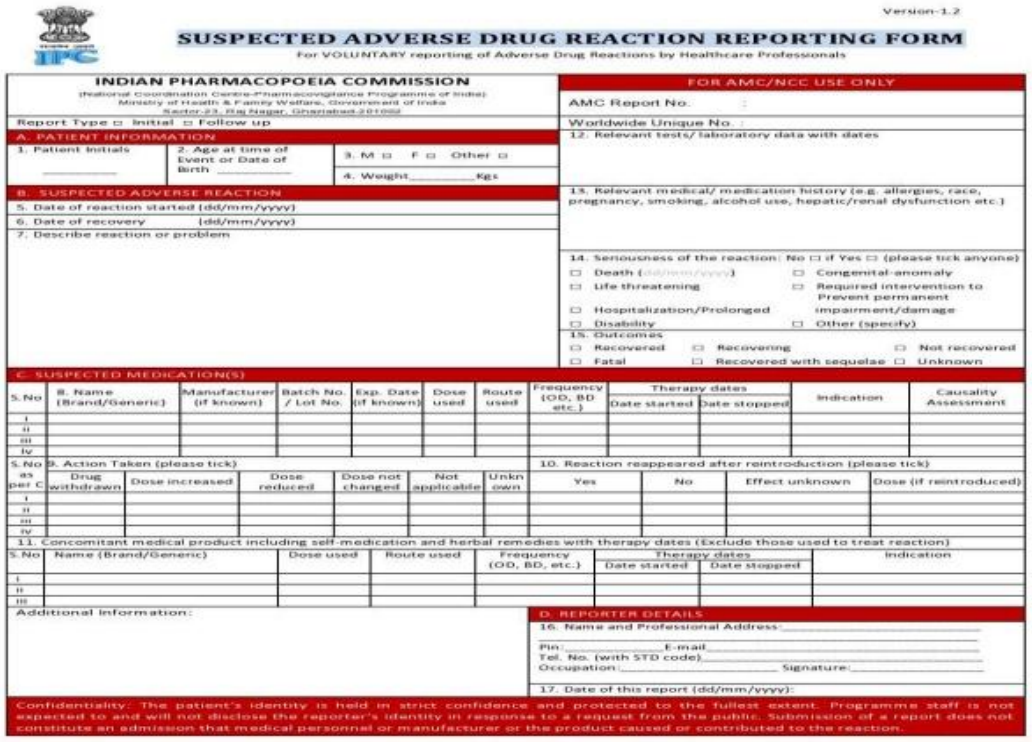
Post-authorization studies (non-interventional);

Worldwide scientific literature (spontaneous, non-interventional);

EudraVigilance data for authorized medicines are analyzed on a regular basis, with a two-week or four-week frequency.

The Pharmacovigilance Risk Assessment Committee (PRAC) evaluates signals from EudraVigilance and may recommend regulatory action as a result.





Version-1.2

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

FOR AMC/NCC USE ONLY

AMC Report No.

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No.

A. PATIENT INFORMATION

1. Patient Initials
2. Age at time of Event or Date of Birth
3. M ☐ F ☐ Other ☐
4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

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

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ If Yes ☐ (please tick anyone)
☐ Death (dd/mm/yyyy) ☐ Congenital anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent impairment/damage
☐ Hospitalization/Prolonged ☐ Other (specify)
☐ Disability

15. Outcomes
☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick): Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Reaction reappeared after reintroduction (please tick): Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

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

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:
Pin: E-mail
Tel. No. (with STD code)
Occupation: Signature:

17. Date of this report (dd/mm/yyyy):

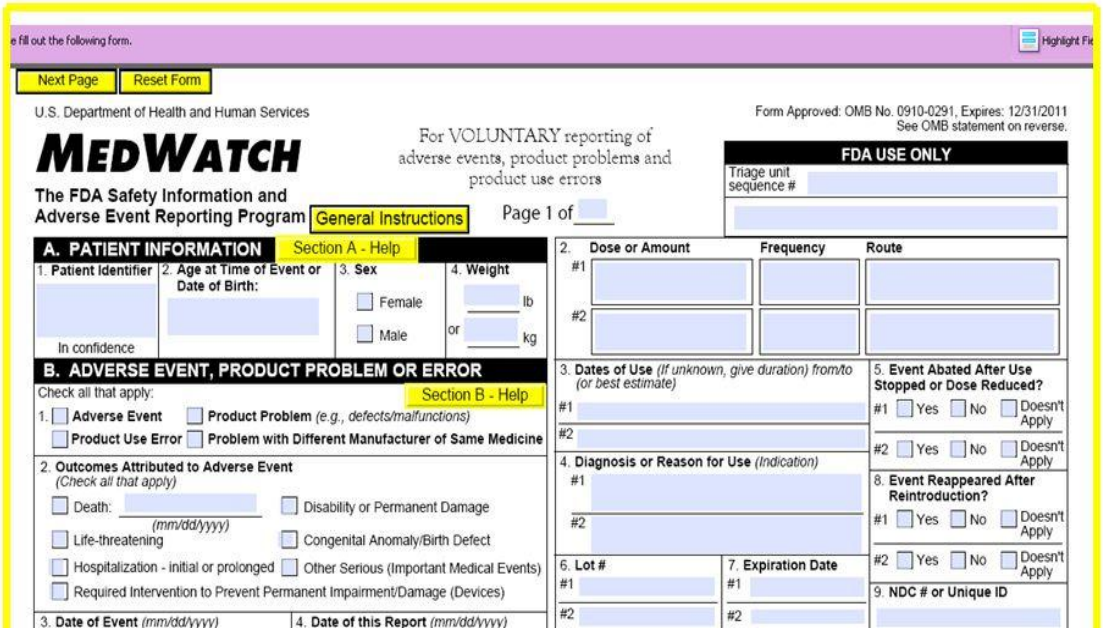
Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

Indian Pharmacopoeia Commission Pharmacovigilance Programme of India

SNM Clinical Trials Network

MedWatch

- FDA Safety Information and Adverse Event Reporting System
- Form FDA-3500



e fill out the following form. Highlight Fie

Next Page Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program General Instructions

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence #

A. PATIENT INFORMATION Section A - Help

1. Patient Identifier — In confidence
2. Age at Time of Event or Date of Birth:
3. Sex: Female / Male
4. Weight: lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR Section B - Help

Check all that apply:

1. Adverse Event ☐ Product Problem (e.g., defects/malfunctions) ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: (mm/dd/yyyy) ☐ Disability or Permanent Damage ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect ☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events) ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)
4. Date of this Report (mm/dd/yyyy)

2. Dose or Amount / Frequency / Route
#1
#2

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis or Reason for Use (Indication)
#1
#2

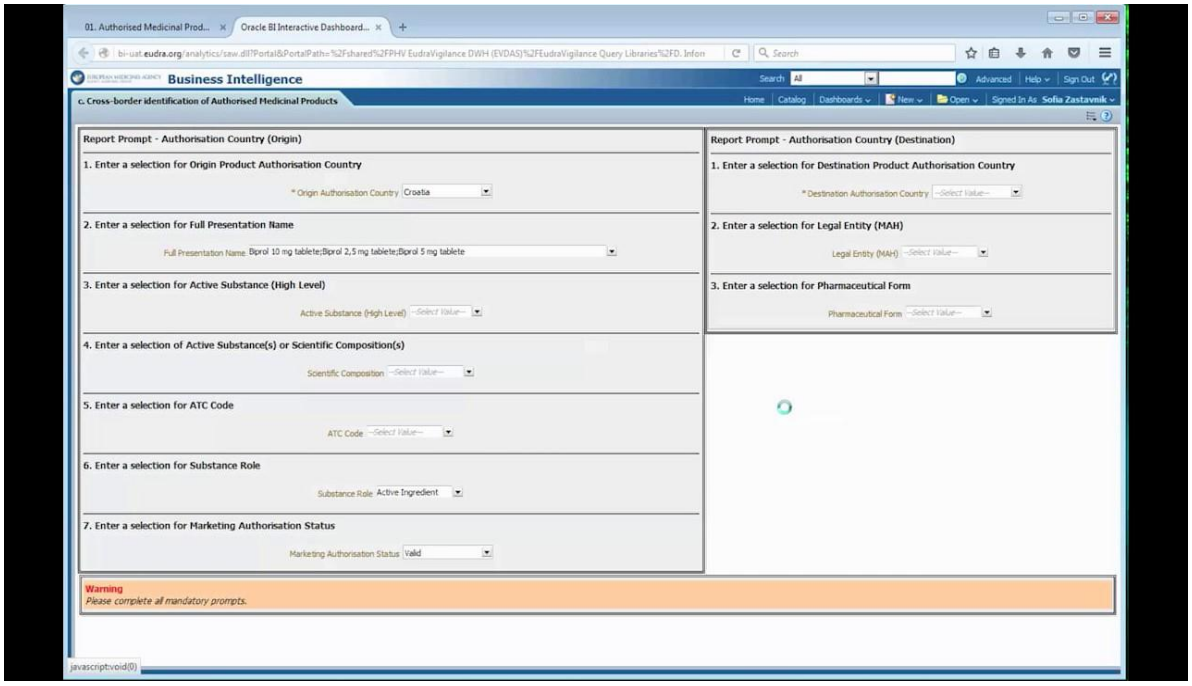
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

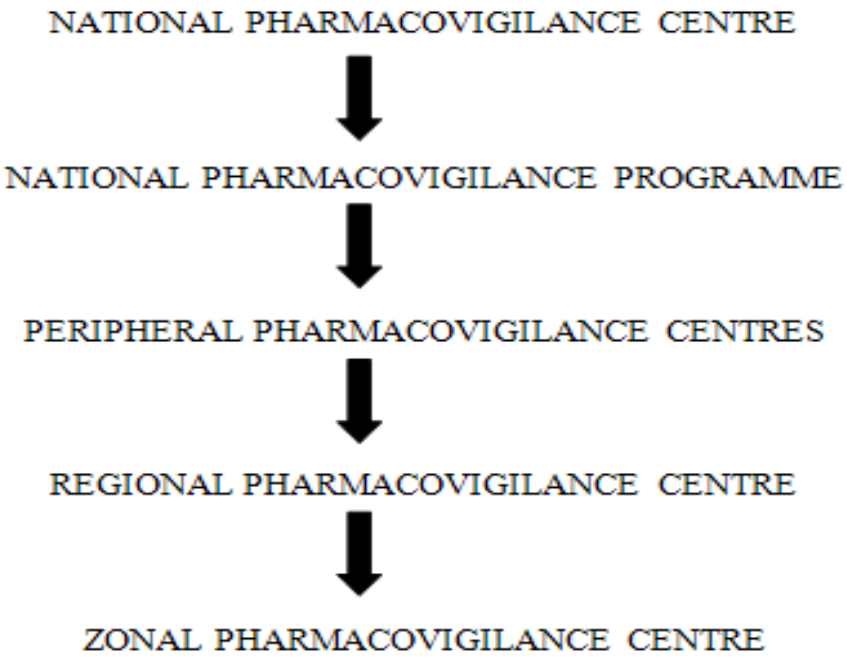
7. Expiration Date
#1
#2

9. NDC # or Unique ID



CONCLUSSION

- Drug toxicity is a relatively common phenomenon—despite a stringent drug safety and clinical trials process, several drugs have been removed from the market being approved by National Drug Regulatory Authorities, including US' FDA, UK's MHRA, and Europe's EMEA [refer to annex of drug withdrawals]. In addition to the removal of potentially toxic drugs from the market, one out of every five drugs is required to add additional warnings related to side? Effects, contraindications, etc. Globally, only about 500,000 to 700,000 adverse event occurrences are captured each year—however, low? To middle? Income countries, which represent more than two? Thirds of the world's population account for a tiny fraction of all the ADR data.
- National Program of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Program of India (PvPI) in 2010. In consideration of having a robust pharmacovigilance system in India, steps were taken. The program is striving hard to build trust between the physician and the patient, thereby increasing patient safety and the confidence of people in the country's health system, in addition to the detection of substandard medicines and prescribing, dispensing and administration errors.
- The IPC-PvPI has now become a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services.
- The below areas should develop in theirs aspects for better pharmacovigilance program in INDIA



- In India Pharmacovigilance (PV) system has increased awareness in people regarding ADR reporting. India is now considered to be a hub for clinical research. The drug control general of India (DCGI) has shown its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. More and more clinical trials are now being conducted in India and business process outsourcing (BPOs) based in India are now also undertaking pharmacovigilance projects from multinational corporations (MNCs).

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