Role of pharmacovigilance in health regulation

Dr Ayesha Rubina[1], Dr Swetha E S[2], Dr Umakanth N Patil[3].

[1,2]PG in Pharmacology, [3]HOD Pharmacology

SS Institute of medical sciences and research centre

DAVANGERE , KARNATAKA. 577004

Pharmacovigilance

- Defined as the “Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines”.

- Pharmakon : “drug”

  Vigilare : “to keep wa

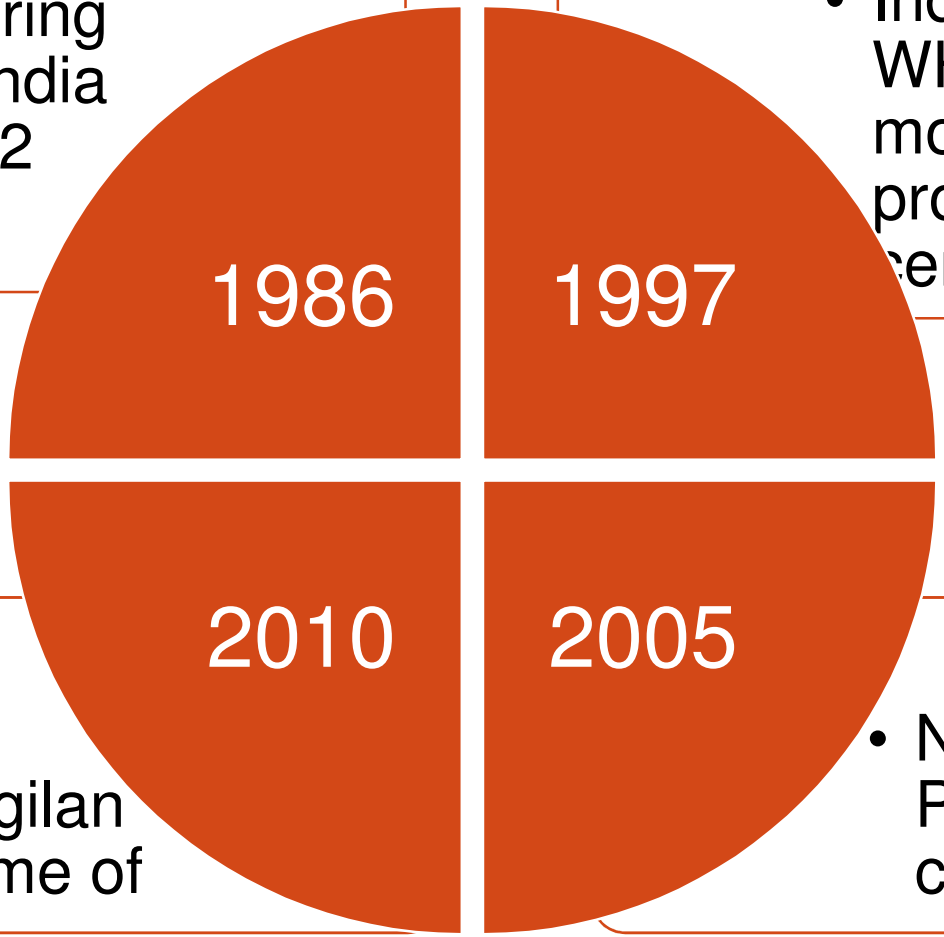
  or “alert”



History

- 1961 phacomelia with the use of thalidomide
- WHO's Programme for International Drug Monitoring was started in 1968.
- Initially 10 countries participated, currently more than 94 countries participate in this programme.
- Coordinated by WHO together with its collaborating centre in Uppsala, Sweden.
- The collaborating center is responsible for maintaining the global ADR database, Vigibase
- Usage of UMC's Vigiflow software for medicines and Paniflow for vaccines
- Access to Vigibase, which contains worldwide medicines safety data

Pharmacovigilance in India : A Brief History



- ADR monitoring system for India proposed (12 regional centers)

- India joined WHO-ADR monitoring programme (3 centers: AIIMS, KEM,JLN

- National Pharmacovigilance Programme of india

- National Pharmacovigilance Programme

Why Pharmacovigilance?

- **Pre-marketing safety data**
  - Animal Experiments : Relevant?
  - Clinical Trials: Complete?
  - Post-marketing Topic **:** Unexpected ADRs, Chronic toxicity, use in special populations(children, elderly or pregnant women) or drug interaction.
- Pharmacovigilance is needed in every country:
  - Distribution and use (eg: indications, dose, availability)
  - Genetics, diet, traditions of the people
  - Pharmaceutical quality and composition(excipients) of locally produced
  - The use of non-orthodox drugs(eg: herbal remedies) which may pose special toxicological

Pharmacovigilance programme of india (PvPI)

- Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Government of India, is functioning as a National Coordinating Centre (NCC) for PvPI since 2011. The centre operates under the supervision of a Steering Committee.

- **Goal**
  - To safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweighs the risks associated with its use

Aims & Objectives



- To improve patient care & safety in relation to medicines & all medical & paramedical interventions.



- To improve public health & safety in relation to the use of medicines

Risk benefit assessment

- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines

Communication

- To promote understanding, clinical training & effective communication to health professionals & the public

How do we know if a patient's condition is an ADR?:

- Take a Proper History and do a proper examination.
- Establish time relationships.
- Do a thorough physical examination with appropriate laboratory investigations.
- Effect of Dechallenge and Rechallenge should be determined. (when necessary).
  - Dechallenge = withdraw of drug
  - Rechallenge = reintroducing the drug after a dechallenge

Causality Assessment

To determine likelihood of a causal relationship between drug exposure and adverse events it is necessary to evaluate

- Association in time/place between drug use and event
- Medical or pharmacological plausibility (signs and symptoms, tests, pathological findings, mechanism)
- Likelihood or exclusion of other causes

- There are assessment scales for causality evaluation which include:
  - Karch and Lasagna scale
  - Naranjo scale
  - WHO probability scale
  - Jones scale

Causality Assessment

- Who Probability Scale:
  - Certain
  - Probable
  - Possible
  - Unlikely
  - Unassessable
- Naranjo method : Questionnaire

What to reported ?

- On an ADR or lack of efficacy connected with the use of a medical device/ drug product.
- ALL suspected drug interactions
- Reactions to any other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing:
  - Life-threatening and death
  - Hospitalization (initial or prolonged)
  - Disability (significant, persistent or permanent)
  - Congenital anomaly
- Required intervention to prevent permanent impairment or damage

When to report

- Any suspected ADR should be reported as soon as possible.
- Delay in reporting will make reporting inaccurate and unreliable.
- If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient

Reporting by whom

- Professionals working in healthcare are the preferred source of information in pharmacovigilance, for example
- Family practitioners,
- Medical specialists and
- Pharmacists,
- Dentists,
- Midwives,
- Nurses and other health workers may also administer or prescribe drugs and should report relevant experiences
- Patient/consumers themself can report ADRs using toll free number: 1800 180 3024 on website

Periodic Safety Update report(PSUR)

- PSURs is submitted every 6 months for the initial 2 years and thereafter annually for the next 2 years. This may be extended by DCGI
- PSURs submitted to DCGI contain cumulative data on the regulatory status information on authorization applications and renewals, as well as data on serious, unlisted adverse reactions.
- must be submitted within 30 calendar days for the last day of the reporting period (Required 30 days after data-lock)
  - Shorter timeline that ICH standard of 60 days

METHODS IN PHARMACOVIGILANCE

1. Passive surveillance:
   a. Spontaneous reports
   b. Case series
2. Stimulated Reporting
   a. Early post marketing phase
3. Active surveillance
   a. Sentinel sites
   b. Drug event monitoring
   c. Registries
4. Comparative observational studies-
   a. Cross sectional study
   b. Case control study
   c. Cohort study
5. Targeted clinical investigations
6. Descriptive studies- Drug utilization studies

1. Passive surveillance

a. **Spontaneous reporting**:

- is an communication by healthcare professionals or consumers to a national pharmacovigilance centre, pharmaceutical company, regulatory authority or other organization(WHO) that describes one or more adverse drug reactions in a patient.
- **Advantages**
  - Early recognition/actual potential problem
  - Provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions
  - Continuous monitoring system
  - Compare ADR profile

b. **Case Series :**

- Provide evidence of an association between a drug and an adverse event, but they are more useful for generating hypotheses than for verifying an association between drug exposure and outcome

2. Stimulated Reporting :

- Include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition.
- The limitations of spontaneous reporting are especially selective reporting and incomplete information.
- Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population.

3. Active surveillance

- Seeks to ascertain completely the number of adverse events via a continuous pre-organised process.

a. **Sentinel sites:**
   - Achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure an accurate data on reported adverse events from these sites.
   - Selection bias, small numbers of patients, and increased costs
   - Eg : Data from specific patient sub-groups.

b. **Registries:**
   - A registry is a list of patients presenting with the same characteristics.

2. Active surveillance

c. Drug event monitoring

- Patients might be identified from electronic prescription data or automated health insurance claims
- A follow-up questionnaire can then be sent to each prescribing physician or patient at prespecified intervals to obtain outcome information
- A modification of Drug Event Monitoring is Cohort Event Monitoring (CEM)
- In CEM, patients on a particular drug are recruited at time of initiation of antiretroviral therapy (ART) and followed up by way of clinic or home visits or where appropriate by phone calls.

4. Comparative Observational Studies

a. Cross-sectional study :
   - Data collected on a population of patients at a single point in time regardless of exposure or disease status.

b. Case-control study: Retrospective study
   - To find association between drug and one specific rare adverse events and to find risk factors.

c. Cohort study : Prospective study
   - Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study.

5. Targeted Clinical Investigations:

- When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction.
- Ex: PK/ PD studies for ADRs, Genetic testing for ADRs, drug-drug interaction studies.

6. Drug utilization studies:

- Drug is marketed, prescribed, and used in a population , and how these factors influence outcomes, including clinical, social, and economic outcomes.

Safety signal

- Safety signal – a concern about an excess of adverse events compared to what would be expected to be associated with a product's use
- Can even be a single AE case, usually a cluster
- Pharmacovigilance primarily looks for safety signals and further analyzes detected signals
- Signals arise from post marketing data which is mainly by PSUR-periodic safety update report.

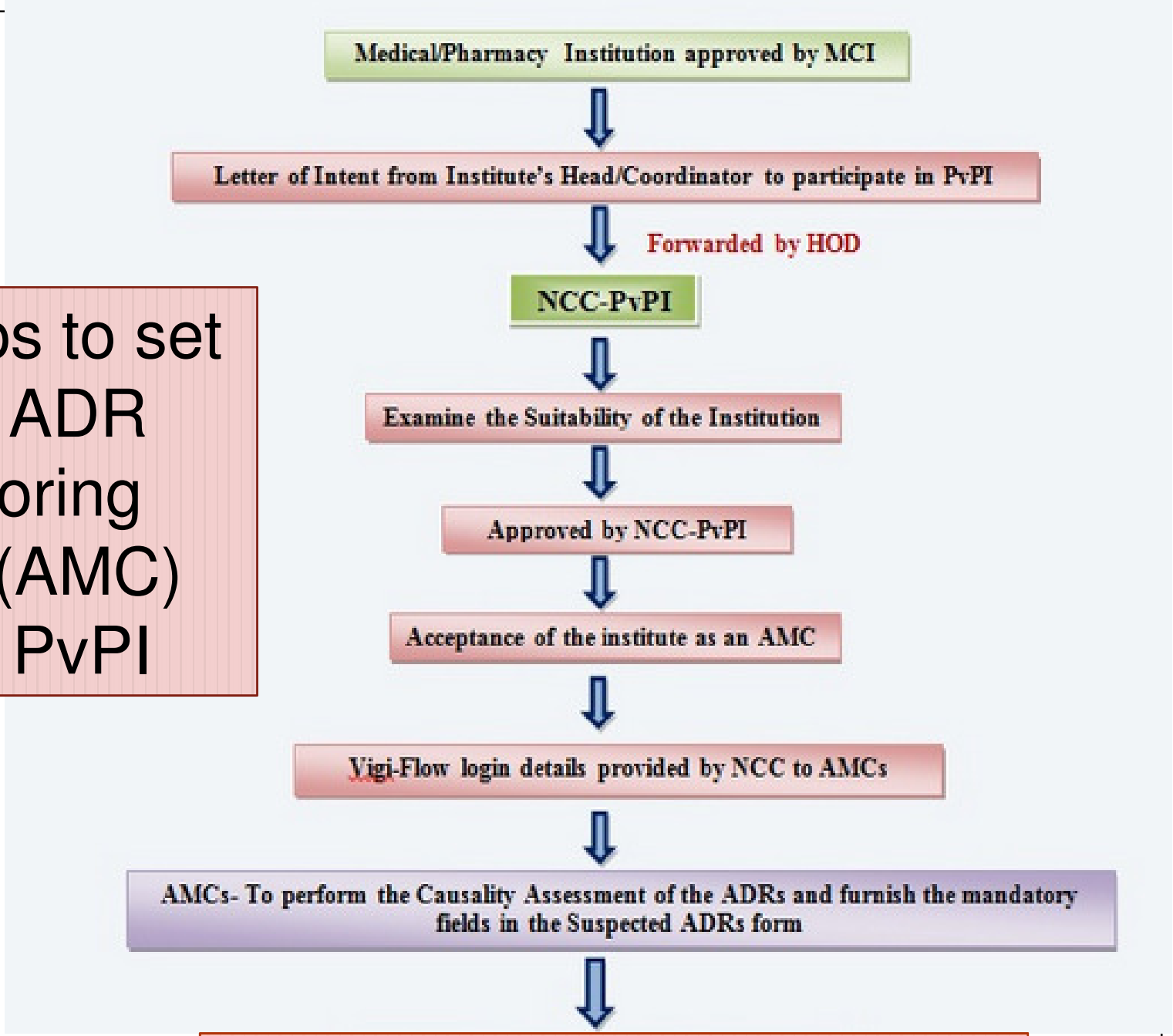
Signal

- A 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”.
- Methods of signal identification
  - Clinical assessment of individual events, Clinical review of collated events , Record linkage, Automated signal detection

Risk management plan

- Once a safety signal has become a true concern:
  - Label changes/boxed warnings, Targeted outreach and education, Product withdrawals
- Risk Management Plan (detect, assess, intervene)

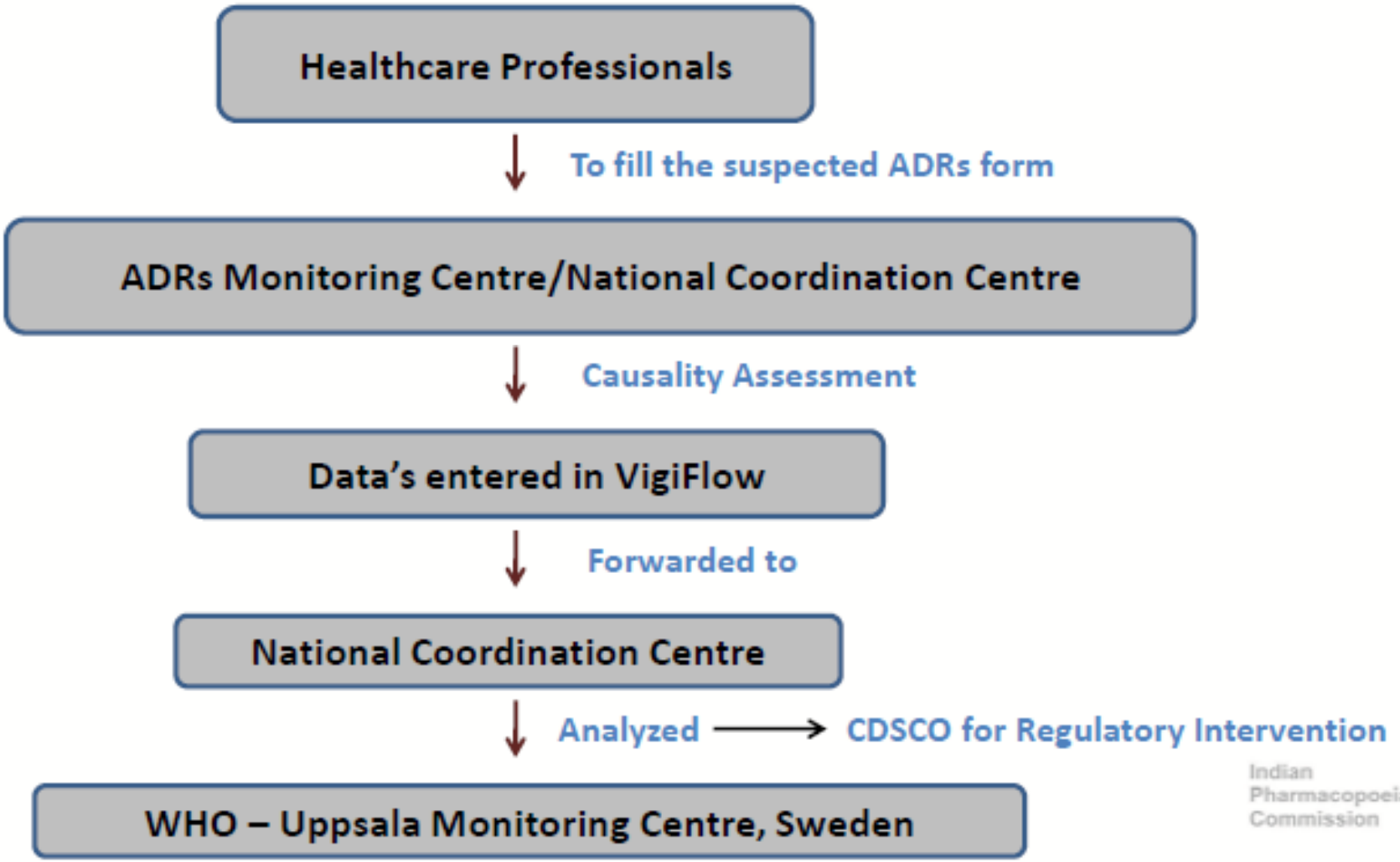
The steps to set up an ADR Monitoring Center(AMC) under PvPI



Functions of the stakeholders in the Programme

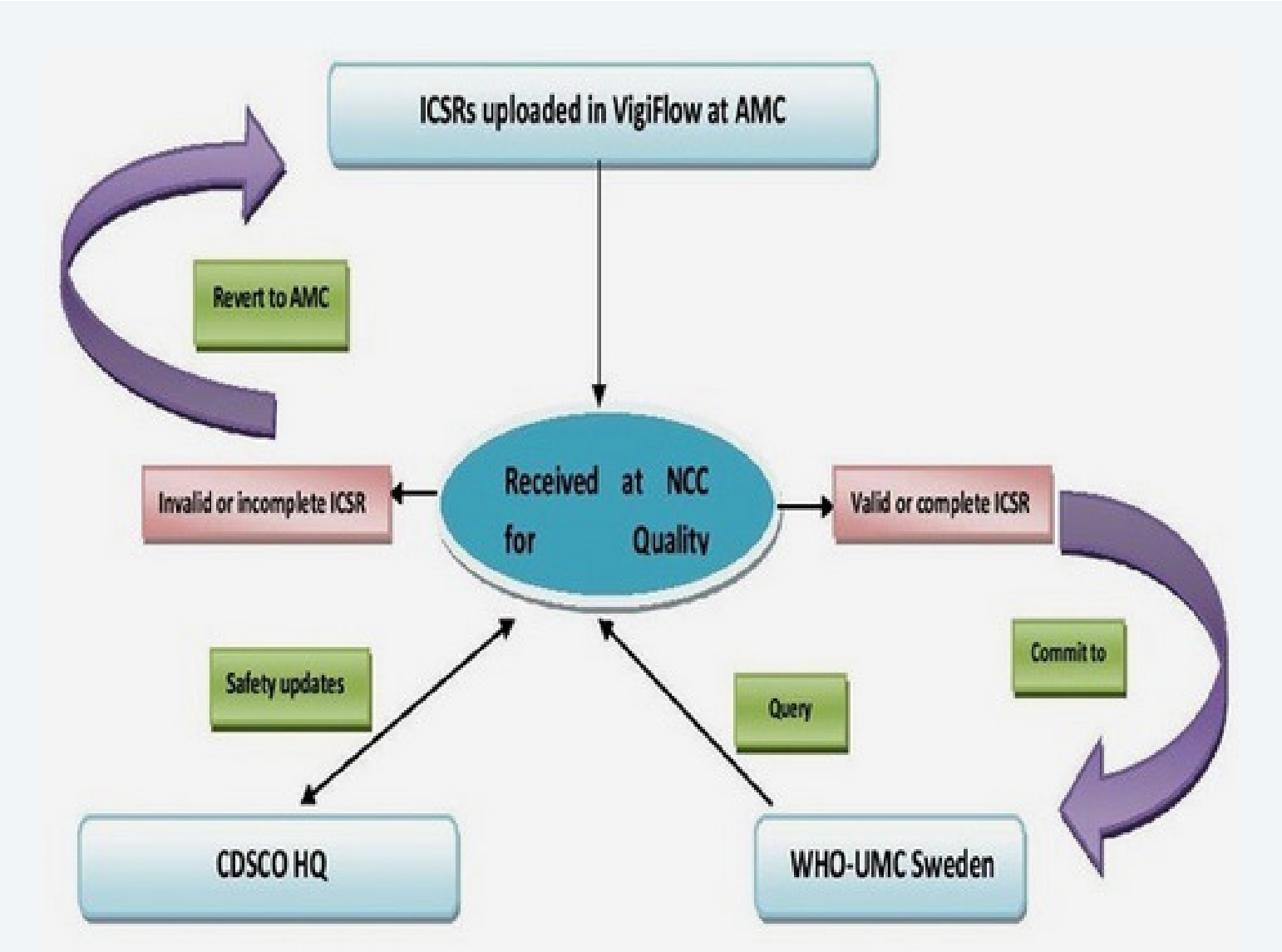
ADRs Monitoring centers	Monitoring and Reporting of ADRs
National Co ordinating Center-PvPI IPC Ghaziabad,UP	• Preparation of SOPs, guidance documents & training manuals • Data collation, Cross-check completeness, Causality Assessment etc as per SOPs • Conduct Training work shops and CMEs • Publication of Medicines Safety News letter • Reporting to CDSCO Head quarters
ZONAL/Subzonal CDSCO Office	• Provide administrative support to ADR monitoring centers
CDSCO, HQ, NewDelhi	• Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC • Propagation of medicine safety related decisions to stake holders

Collation, analysis and evaluation of ADRs

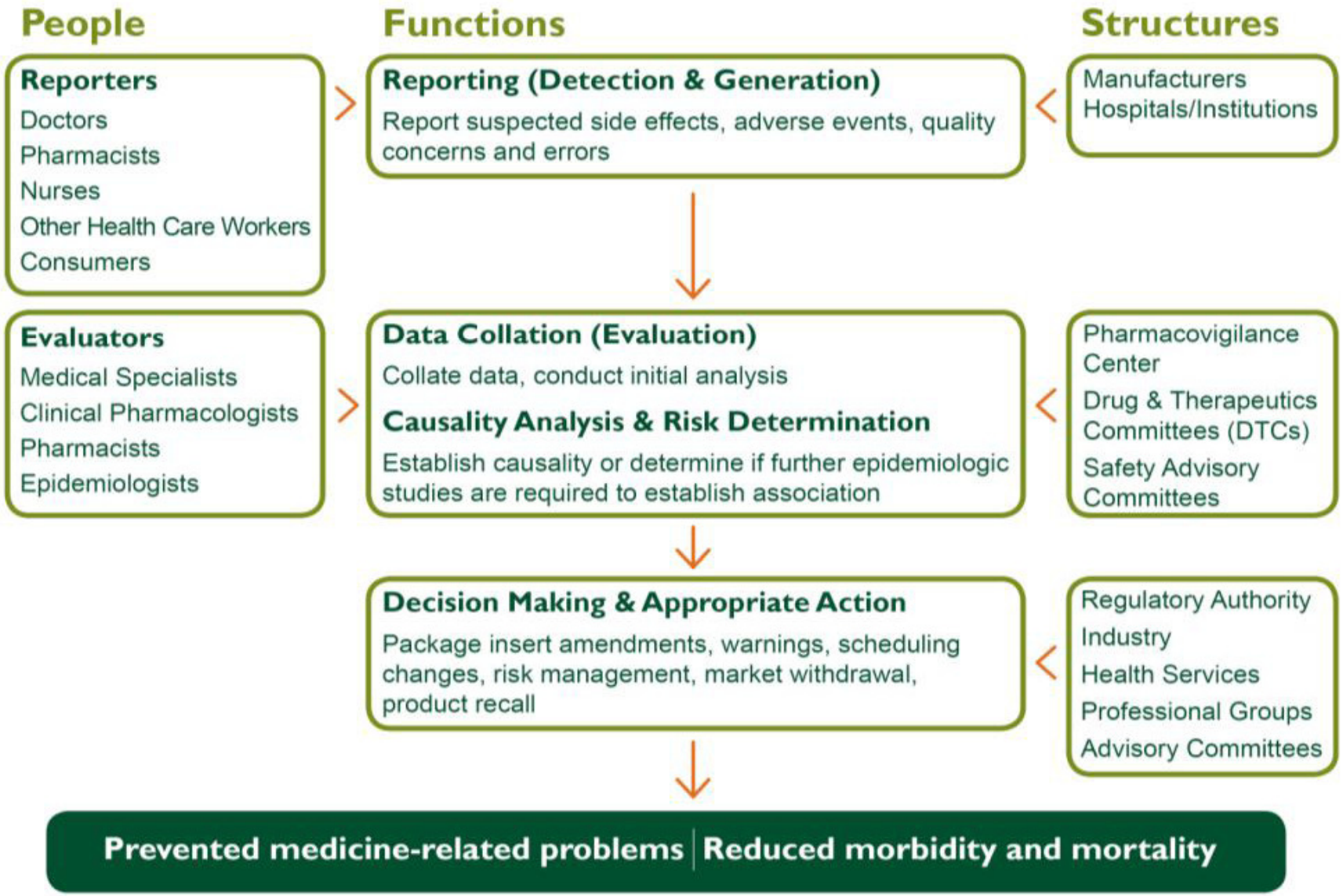


Indian Pharmacopoeia Commission

Vigiflow Reporting System.



Pharmacovigilance framework



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

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. 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
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ 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)		Reason for use of prescribed for
								Date started	Date stopped	
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)

Recently banned drugs in India

Technical inputs for the regulatory intervention

- Pioglitazone
- Analgin
- Dextropropoxyphene
- Fixed dose combination of Flupentixol+Melitracen

Recommended Drug Safety Information to issue Drug Alerts

Sl no	Name of the Drug	Recommended drug alerts in
1	Methotrexate	Liver fibrosis
2	Montelukast	Neuropsychiatric risk
3	Ceftriaxone	Hepatitis
4	Leflunomide	Steven johnsons syndrome

Summary

- India is one of the largest producer of pharmaceuticals and emerging as an important clinical trial hub in the world.
- With introduction of new drugs, a robust pharmacovigilance system is needed to protect the population from the potential harm and adverse effect due to some of the new drug molecules.
- Pharmacovigilance plays a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines.
- ↑ awareness and training of public and medical professions, framing of strong regulations for reporting of ADRs, effective implementation and collaborative efforts between government, regulatory officials, pharmaceutical companies, health care professionals and patient may lead to an effective

Thank you

References

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