Pharmacovigilance to Ensure Safe Medication

Dr. Subhash C. Mandal

Member, National Working Group
Pharmacovigilance Programme of India

E mail:subhash.mandaldr@gmail.com

Disclaimer

The views expressed in this presentation is personal views of the presenter. In no way it is the views of the organization to which the presenter is associated.

Medicine Safety

“To undergo treatment you have to be very healthy, because apart from your sickness you have to withstand the medicine”

Molière

Pharmacovigilance

What is Pharmacovigilance?

"Pharmacovigilance"

Pharmacon (Greek)-Drug

+

Vigilare (Latin)-to keep watch

WHO Definition

The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems.

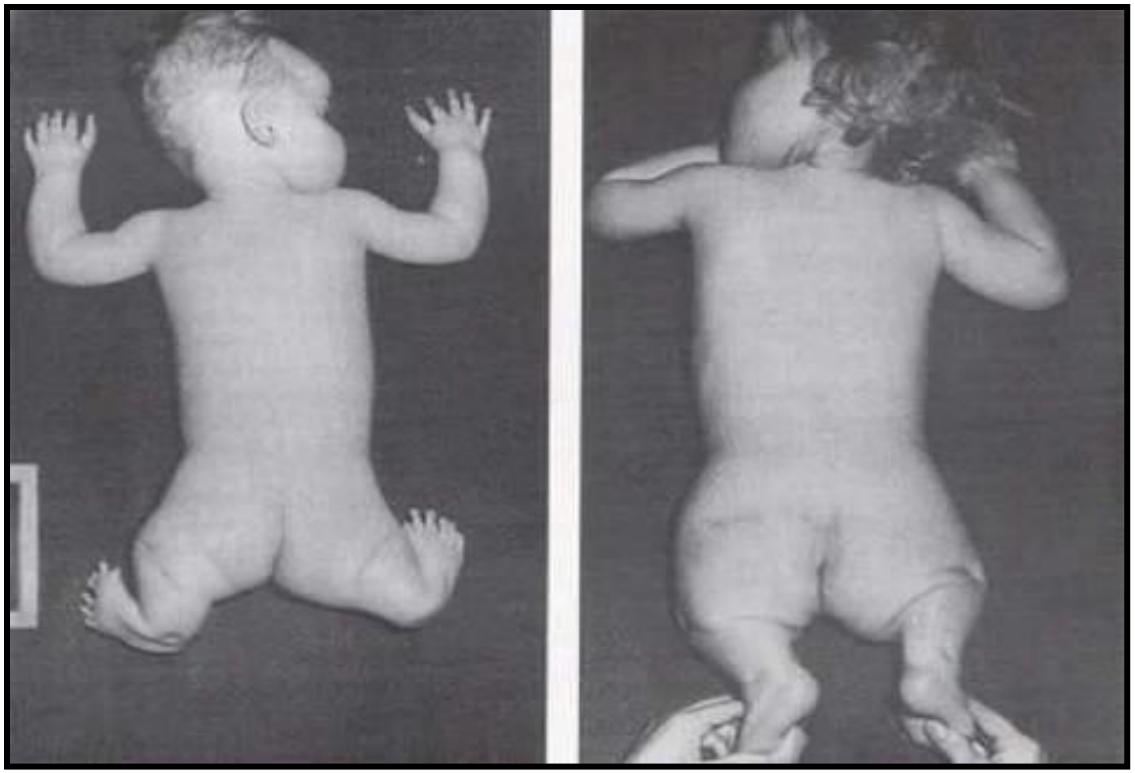
Why Pharmacovigilance?

- **Humanitarian concern –**
  - Insufficient evidence of safety from clinical trials
  - Animal experiments
  - Phase 1 – 3 studies prior to marketing authorization
- limited size: no more than 5000 and often as little as 500 volunteers
- narrow population: age and sex specific
- narrow indications: only the specific disease studied
- short duration: often no longer than a few weeks

Why Pharmacovigilance?

Post Marketing Topics

- Unexpected adverse reactions
- Interactions
- Risk factors
- Quality of life (QOL)
- Long-term efficacy
- Cost assessment



Examples of product recalls due to toxicity

Medicine	Year	Examples of serious and unexpected adverse events leading to withdrawal of medicine
Thalidomide	1965	Phocomelia
Practolol	1975	Sclerosing peritonitis
Clioquinol	1970	Subacute nephropathy
Benoxaprofen	1982	Nephrotoxicity, cholestatic jaundice
Terfenadine	1997	Torsade de pointes
Rofecoxib	2004	Cardiovascular effects
Veralipride	2007	Anxiety, depression, movement disorders

Impact of ADR on health care system

- ***Medicines are supposed to save lives***

  Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable. Lepakhin V. Geneva 2005

- US:

  Adverse Drug Reactions are among the **top ten** causes of mortality, (Lazarou J. et al., 1998)

- UK:

  It has been suggested that ADRs may cause 5700 deaths per year in UK, (*Pirmohamed et al, 2004)*

- The percentage of hospital admissions due to drug related events in some countries is about or more than 10% *(Bhalla et al, 2003; Imbs et al, 1999)*

Economic Impact of ADR

ADRs are expensive !!

US situation

- Cost of drug related morbidity and mortality exceeded $177.4 billion in 2000 (*Ernst FR & Grizzle AJ, 2001: J American Pharm. Assoc)*
- ADR related cost to the country exceeds the cost of the medications themselves

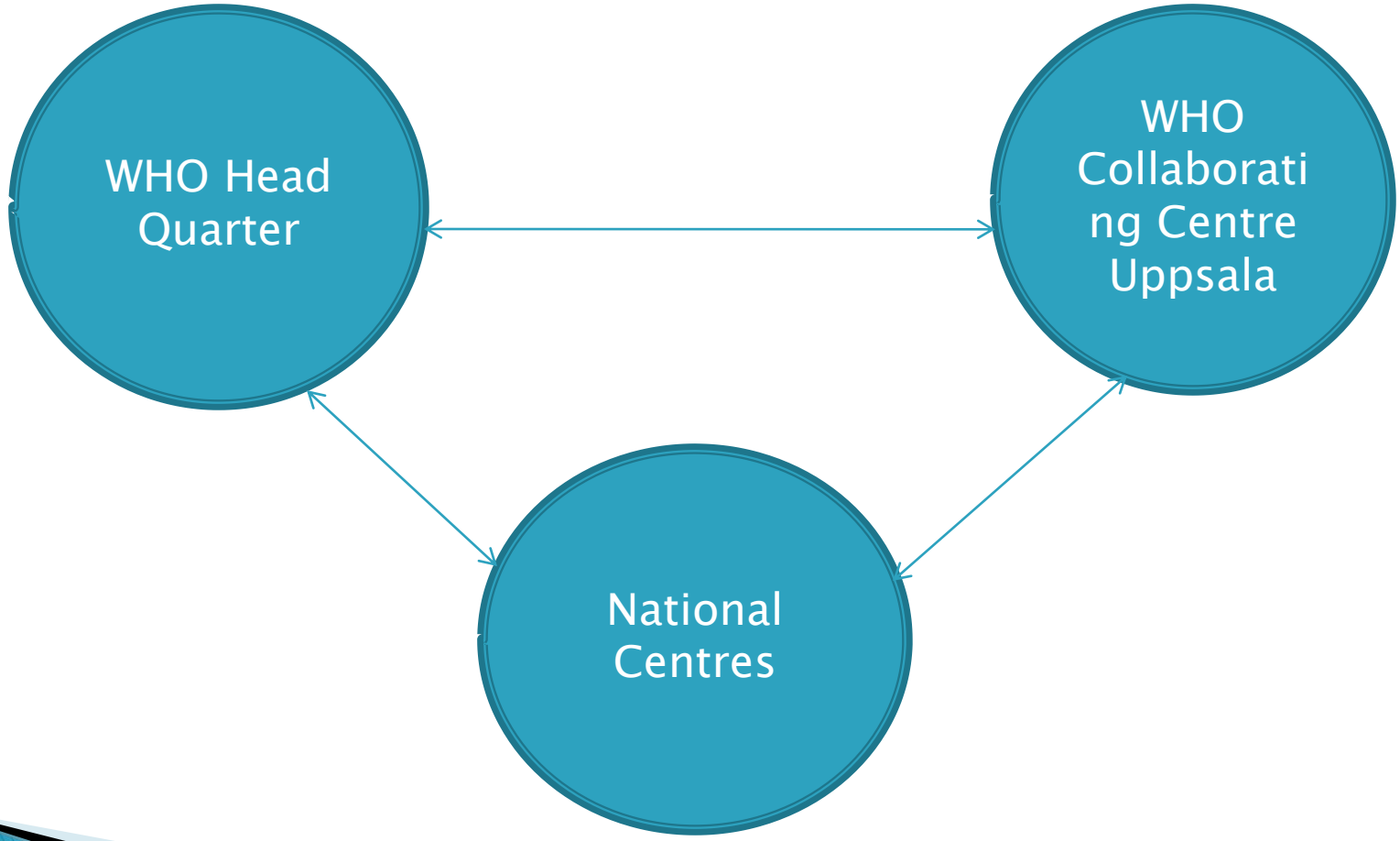
Pharmacovigilance

Major Aims

- early detection of unknown safety problems
- detection of increases in frequency
- identification of risk factors
- quantifying risks
- preventing patients from being affected unnecessarily

Rational and Safe use of Medicines

WHO Programme for International Drug Monitoring



Pharmacovigilance programme of India (PvPI)

History

- 700 BC: Charak Samhita-Caution that properly understood but improperly administered drug is like a poison
- 500 AD: Vagbhatta-a physician described adverse events, contraindication, delayed ADRs to Ayurvedic Drugs
- Published literature reports of ADRs from India are found in the history of modern medicine but there was no systematic effort for ADR monitoring

Why ADR monitoring in India?

- Besides ethnic, nutritional, disease prevalence and genetic differences, variation in prescribing practices affect benefit risk ratio e.g. Pioglitazone is banned in some developed countries due to high occurrence of bladder cancer, whearas is not banned in India due to low occurrence of bladder cancer

First attempt-1989

- Initiative: DCGI started ADR monitoring at 6 centres-Delhi, Mumbai, Calcutta, Lucknow, Chandigarh & Pondichery
- Purpose: Spontaneous reporting, intensive hospital monitoring and focused reporting
- India Joined the WHO UMC monitoring programme in 1998
- National Pharmacovigilance centre-AIIMS, Delhi
- WHO special centre-GS Sheth Medical College KEM Hospital, Mumbai

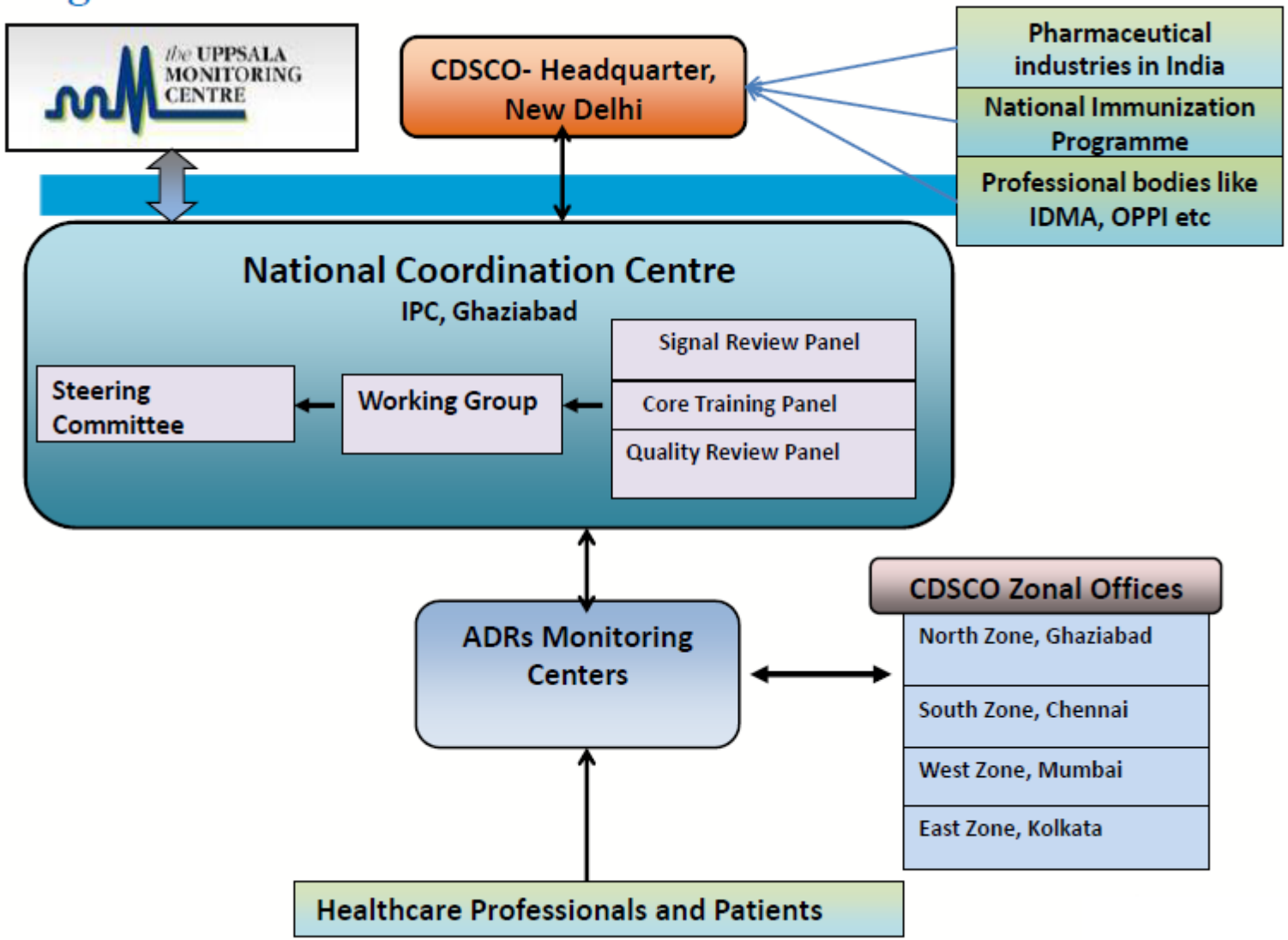
Second attempt-2004

- World Bank aided Pharmacovigilance programme
- National Pharmacovigilance centre
- Pharmacovigilance advisory committee
- Two zonal centres-Nort East at AIIMS Delhi & South West at GSMC KEM Mumbai
- Four regional centres-North, East, South & West
- Peripheral centres
- Mumbai Centres was sending ADRs to WHO UMC

Ongoing PvPI programme

- Started in July 2010
- Under CDSCO, Ministry of Health & Family Welfare with NCC at AIIMS, New Delhi
- NCC was shifted to Indian Pharmacopoeia Commission, Gaziabad in April 2011
- Dr. G.N.Singh as the member Secretary

Programme Communications



Functions of the stakeholders in the Programme

ADRs Monitoring Centers	• Monitoring and Reporting of ADRs
NCC-PvPI IPC Ghaziabad, UP	• Preparation of SOPs, guidance documents & training manuals • Data collation, Cross-check completeness, Causality Assessment etc as per SOPs • Conduct Training workshops and CMEs • Publication of Medicines Safety Newsletter • Reporting to CDSCO Headquarters
ZONAL/Subzonal CDSCO Offices	• Provide administrative support to ADR monitoring centers
CDSCO, HQ, New Delhi	• Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC • Propagation of medicine safety related decisions to stakeholders

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. :

Worldwide Unique No. :

Report Type ☐ Initial ☐ Follow up

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
☐ Disability ☐ Other (specify)

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		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
Iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	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		Indication
					Date started	Date stopped	
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.

WHO ART / MEDRA

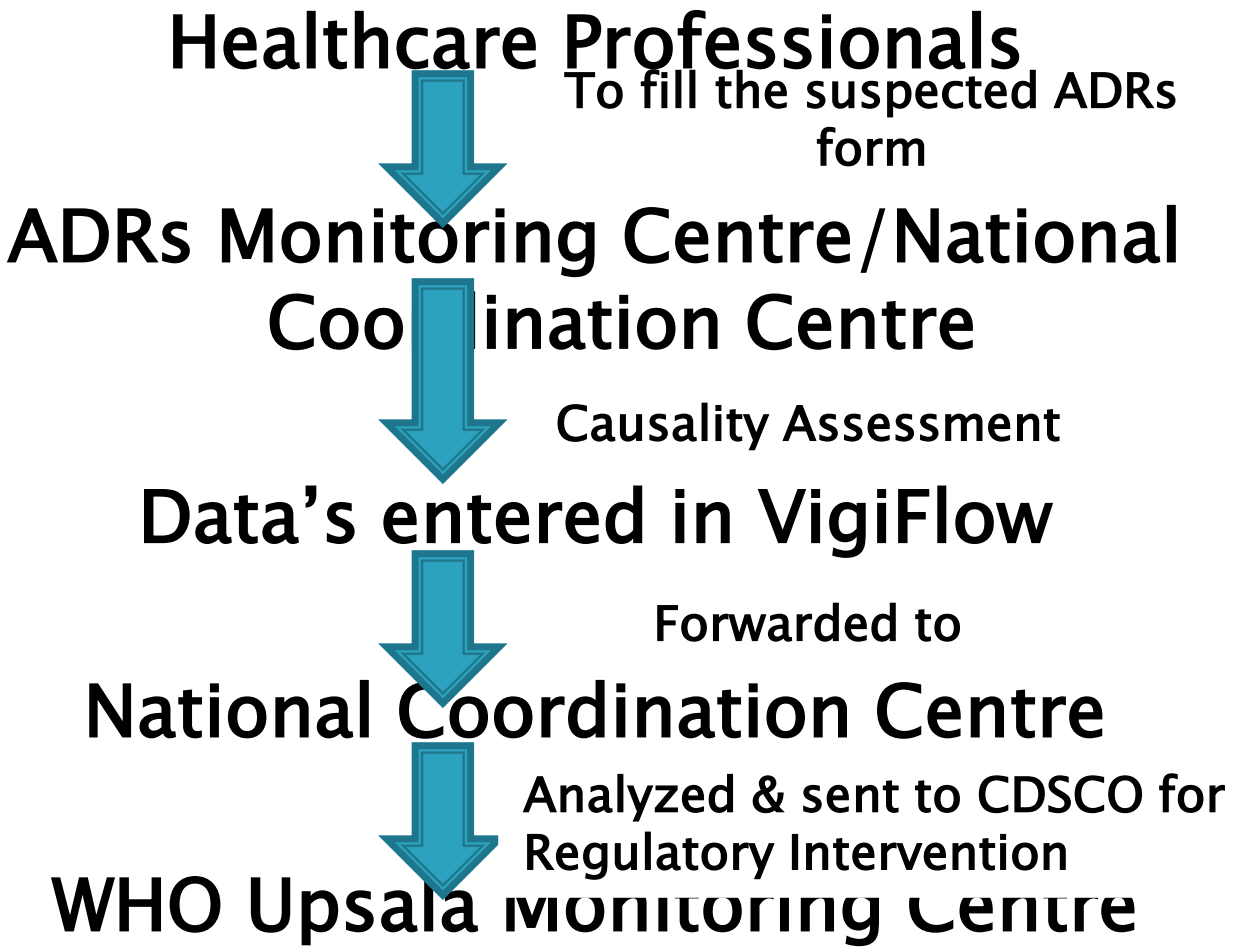
WHO ART

- The WHO Adverse Reaction Terminology – WHO-ART Terminology for coding clinical information in relation to drug therapy

MEDRA

- Medical Dictionary for Regulatory Activities: terminology created under the auspices of the International Conference on Harmonisation (ICH) and owned by the International Federation of Pharmaceutical Manufacturers Association (IFPMA) acting as trustee of the ICH steering committee.

Collation, analysis and evaluation of ADRs



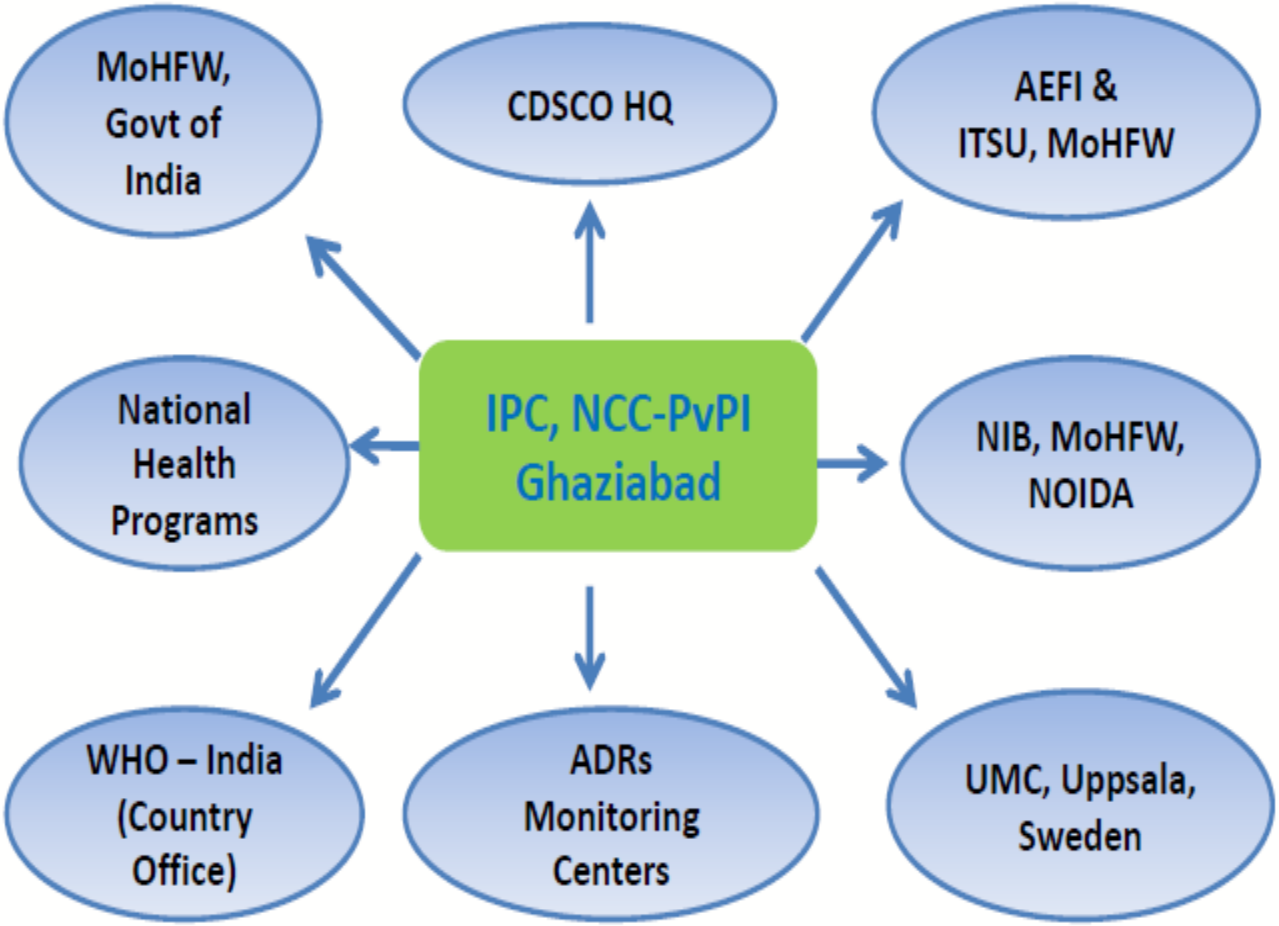
Parallel Programmes

- **Haemovigilance (HvPI):** Started since 10th Dec. 2012 in collaboration with National Institute of Biologicals (NIB)
- **Materiovigilance (MvPI):** Started since 6th July 2015. IPC as National Coordinating Centre & Sree Chitra Tirunal Institute of Medical Sciences & Technology (SCTIMST) is functioning as National Collaborating Centre. National Health Systems Resource Centre (NHSRC) under MoHFW, Govt. of India working as technical support and resource centre

Regulatory action on the basis of ADR reports

Drug	ADR	PvPI outcome	CDSCO action
Carbamazepine	Stevens Johnson Syndrome and Toxic Epidermal Necrolysis	For drug safety Label Change-Patient may be screened for HLA-B*1502 prior to use Carbamazapine	CDSCO requested all State/ UT Drugs Controllers to instruct all MHAs for inclusion of “SJS and TEN” in the same prescribing information and same should be available on the MHA website (F.No.12-01/15/DC (Pt-23) dtd. 12.05.2015
Piperacilline & Tazobactam	Hypokalaemia and Bronchospasm	To include in PIL	CDSCO requested all State/ UT Drugs Controllers to instruct all MHAs for inclusion of the same prescribing information and be available in the MHAs website
Ranitidine	Cardiac Arrest	To include in PIL	CDSCO requested all State/ UT Drugs Controllers to instruct all MHAs for inclusion of “Cardiac Arrest ” in the same package insert / promotion literature
Proton Pump Inhibitors (PPIs)	Acute Kidney injury	To include in PIL	CDSCO requested all State/ UT Drugs Controllers to instruct all MHAs for inclusion of “Acute Kidney injury” in the same package insert / promotion literature (F.No.12-01/18-DC (Pt-337) dtd. 04.11.2019

Collaboration of NCC-PvPI with other Organizations



Gazette Notification G.S.R. 287 (E) dtd. 08.03.2016

- **Schedule Y**
- **(4) Post Marketing Surveillance.-** I) The applicant shall have a pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for information on adverse drug reactions emerging from the use of the drugs manufactured or marketed by the applicant in the country.
- Ia) The system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.
- Ib) Subsequent to approval of the product, new drug shall be closely monitored for its clinical safety once it is marketed.
- Ic) The applicant shall furnish Periodic Safety Update Reports (PSURs) in order to- (a) Report all relevant new information from appropriate sources; (b) Relate the data to patient exposure; (c) Summarise the market authorisation status in different countries and any significant variations related to safety; and (d) Indicate whether changes shall be made to product information in order to optimise the use of product."

New Drug and Clinical Trial Rules 2019

Post marketing assessment of new drug

- When-
- A new drug manufacturing and marketing
- A new drug import and marketing
- The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports

Post marketing surveillance

- The periodic safety update reports shall be submitted every six months for the first two years after approval of the drug is granted to the applicant.
- For subsequent two years – the periodic safety update reports need to be submitted annually.
- Central Licencing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health.
- Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licencing authority within fifteen days of initial receipt of the information by the applicant.
- If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

Pharmacovigilance Guidance Document

for

Marketing Authorization Holders of Pharmaceutical Products

Published by

Indian Pharmacopoeia Commission
National Coordination Centre - Pharmacovigilance Programme of India
in Collaboration with Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India

Complaints and Adverse Reactions

- 28.1. All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.
- 28.2. Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.
- 28.3 There shall be written procedures describing the action to be taken, recall to be made of the defective product.

Conclusion

- ADR has major impact on health-Social, QoL and financial
- Each stake holders have its definite role to play
- Pharmacovigilance providing data to act by all stake holders in healthcare system including regulators
- PvPI playing a vital role in the area of medication safety……

Helpline Number Managed by NCC PvPI to provide assistance in ADRs reporting for the HCPs and general public: 1800 180 3024 (All Working Days 9:00 AM to 5:30PM)

Thank You