ISSUE No. 35

SILVER JUBILEE YEAR 2016

TAMILNADU PHARMACEUTICALS SCIENCES WELFARE TRUST

25 Years

## Special Issue : Pharmacovigilance Training Programme

# Pharma Web

## Newsletter of Tamilnadu Pharmaceutical Sciences Welfare Trust

Jul. - Aug. - Sep. 2017

# Delvin Formulations

*Destiny for Innovation*

# Moving Globally

- R & D and Manufacturing of API
- R & D and Manufacturing of Formulations
- International Marketing
- Domestic Marketing
- Medical Devices
- Surgicals


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Tamilnadu Pharmaceutical
Sciences Welfare Trust

# Pharma Web

## Newsletter of Tamilnadu Pharmaceutical Sciences Welfare Trust

ISSUE : 35 Jul. - Aug. - Sep. 2017



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TAMILNADU PHARMACEUTICAL SCIENCES WELFARE TRUST
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# EDITORIAL

Dear Readers,

Wishing you all a very Happy Deepavali.

We are happy to publish the 35th issue of Pharma Web Newsletter for Jul – Sep 2017.

We regret to inform the delay in publishing this issue, due to preoccupation in organizing various training programmes to fresh Pharmacy graduates. We wish to inform our readers, the Pharma Knowledge and Training Institute (PKTI), conducted a new training programme on the subject of Pharmacovigilance for M. Pharm and Pharm D students during 3rd to 5th August 2017. The faculties were drawn from a renowned Medical Institutions from Tamilnadu, Puducherry, and Karnataka. The programme was supported by Dr. V. Kalaiselvan, Principal, Scientific Officer, IPC, CDSCO. Delhi. The highlights of the programme including the lectures given by the faculties are featured in this issue.

This Newsletter contains all the lectures like, objective of Pharmacovigilance, Terminology involved in Pharmacovigilance, Adverse Drugs Reaction / Adverse Events and its important, Role of healthcare professional in Pharmacovigilance and setting up of Pharmacovigilance system etc.,

The PKTI also conducted 5th Industrial Orientation Training Programme for fresh Pharmacy graduates during the month of September 2017. The highlights of this programme will be published in the next issue.

The Newsletter also contain various events like Pharmacist Day Celebration, programmes of IPA TN Branch etc.,

We are very much thankful to M/s. Fourrts (India) Laboratories Pvt. Ltd., M/s. Delvin Formulations, M/s. Medopharm, M/s. Tablets (India) Ltd., for the continuous support by giving advertisement, in order to sustain the cost of publishing of this newsletter.

Hope this Newsletter will benefit our Pharma professionals. Any suggestions to improve our news letter are welcome.

*With Best Regards,*
**R. NARAYANASWAMY**
*Chief Editor*

# PHARMA KNOWLEDGE AND TRAINING INSTITUTE (FINISHING SCHOOL)

## Pharmacovigilance Training Course

Tamilnadu Pharmaceutical Sciences Welfare Trust has started a training institute under the name of "Pharma Knowledge and Training Institute (PKTI) – Finishing School" with the objective to train fresh Pharmacy Graduates in order to impart knowledge and better placement in Pharma Industries and allied fields. We are conducting the series of training in Industrial Orientation Training for fresh graduates and final years of B. Pharm and M. Pharm. Now we have conducted another programme in Pharmacovigilance for Pharm D students. This was organised with the help of Indian Pharmacopoeia Commission, Ghaziabad under the guidance of Dr. V. Kalaiselvan.

The Pharmacovigilance Training course held form 3rd August to 5th August 2017. The trainees are final year Pharm D students from SRM University, Sri Ramachandra University, Vels University, C. L. Baid Metha College of Pharmacy, K. K. College of Pharmacy, Chennai & Vinayaka Mission's College of Pharmacy, Salem. A total of 50 students were trained in this programme. A formal inauguration of this programme was held on 3rd August 2017. Mr. S. V. Veerramani, CMD, M/s. Fourrts (India) Laboratories Pvt Ltd., Chennai, President IDMA, inaugurated the programme. In his inaugural address, he emphasized the need of setting up Pharmacovigilance system in Pharmaceutical companies. He also said that this programme will be useful to the Pharm D students who take up the carrier of Pharmacovigilance system. Mr. R. Srinivasan, Vice-Chairman of C. L. Baid Metha College of Pharmacy, Chennai that the Pharmacovigilance system need to be improved in our country from retail chemist to the level of doctors and Pharmaceutical manufacturers and consumers. He also said that such programme will be beneficial for the community. Dr. G. Parthasarathi, JSS University Mysuru and Dr. Guru Prasad Mohanta of Annamalai University narrated the objective of this programme and empowering the knowledge of the Pharm D students.

The following faculties gave lecture on the relevant topics mentioned below.

| S.No | Topic | Speaker |
|---|---|---|
| | **3rd August 2017** | |
| 1 | Basic, Introduction & Objectives of Pharmacovigilance | Dr. G. Parthasarathi<br>Dean, Global Engagement, Professor, Pharmacy Practice, JSS University, Mysuru |
| 2 | Terminology & Involving Pharmacovigilance and methods of Adverse Event Reports | Mr. Krishna Undela<br>Lecturer – Dept of Pharmacy Practice, JSS University, Mysuru |
| 3 | Adverse Events: What, Where & When to report | Dr. K. M. Sudha,<br>Professor of Pharmacology,Coordinator -(PvPI)<br>Madras Medical College, Chennai |
| 4 | Role of Healthcare professionals including Pharmacist in Pharmacovigilance | Dr. Guru Prasad Mohanta,<br>Professor, Department of Pharmacy, Annamalai University, Chidambaram |
| 5 | Effective communication setting up of Pharmacovigilance system | Dr. G. Parthasarathi<br>Dean, Global Engagement, Professor,<br>Pharmacy Practice, JSS University, Mysuru |
| | **4th August 2017** | |
| 1 | Introduction to various Adverse Drug Reaction reporting forms including Pharmacovigilance programme | Ms. Siddiraju Devipriya<br>Patient Safety - Pharmacovigilance Associate, PvPI, Madras Medical College, Chennai |
| 2 | Transcription of data case study to reporting form (Hands on Training) | Mr. C. Stalin,<br>Patient Safety- Pharmacovigilance Associate (PSPvA), PvPI Kilpauk Medical College, Chennai |
| 3 | ADR / AE & its clinical Relevance | Dr. Lourdu Jafrin. A<br>Associate Professor and Head<br>Dept. of Pharmacology<br>IGMC&RI, Puducherry |
| 4 | Logistic methodology of causality of Assessment (Group Exercise) | Dr. S. Sandhiya,<br>Assistant Professor, Dept of Clinical Pharmacology, JIPMER, Puducherry |

## Inauguration of Pharmacovigilance Training Programme



## Lecture and Felicitation to Dr. G. Parthasarathi



## Lecture by Mr. Krishna Undela

## Felicitation to Dr. K. M. Sudha

## Lecture by Dr. Guru Prasad Mohanta


## Felicitation to Ms. Siddiraju Devipriya


## Felicitation to Mr, C. Stalin


## Lecture by Dr. A. Lourdu Jafrin


## Lecture and Felicitation to Dr. S. Sandhiya


## Trainees of the Pharmacovigilance



## Lecture & Felicitation to Dr. V. Kalaiselvan



## Felicitation to Dr. S. Manivannan


## Felicitation to Dr. C. Ramachandra Bhat

**Group Photo of Trust Members with Faculties**

**Certificate issue to the trainees**


**Certificate issue to the trainees**


**Certificate issue to the trainees**


**Certificate issue to the trainees**


**Group photo of Trustees, Faculties & Trainees**

| S.No | Topic | Speaker |
|---|---|---|
| | **5th August 2017** | |
| 1 | Pharmacovigilance programme in India & its Regulatory implication | Dr. V. Kalaiselvan<br>Principal Scientific Officer, Indian Pharmacopoeia Commission, Ghaziabad |
| 2 | Regulatory aspect of Pharmacovigilance | Dr. S. Manivannan,<br>Deputy Drug Controller of India, CDSCO Chennai |
| 3 | Role of CDSCO in Pharmacovigilance | Dr. S. Manivannan,<br>Deputy Drug Controller of India, CDSCO Chennai |
| 4 | Integration of National Health programs in Pharmacovigilance | Dr. C. Ramachandra Bhat,<br>Prof and HOD, Dept of Pharmacology & Coordinator, Regional Pharmacovigilance Centre, Kilpauk Medical college, Chennai |

The training programme was concluded with the issue of certificate to the trainees. The students who attended the programme have given the feedback that such similar programmes enriched them with knowledge for their future carrier. They appreciated the faculties and also the initiative of our Trust for conducting such programmes. They also commented such programme need to be organised frequently.

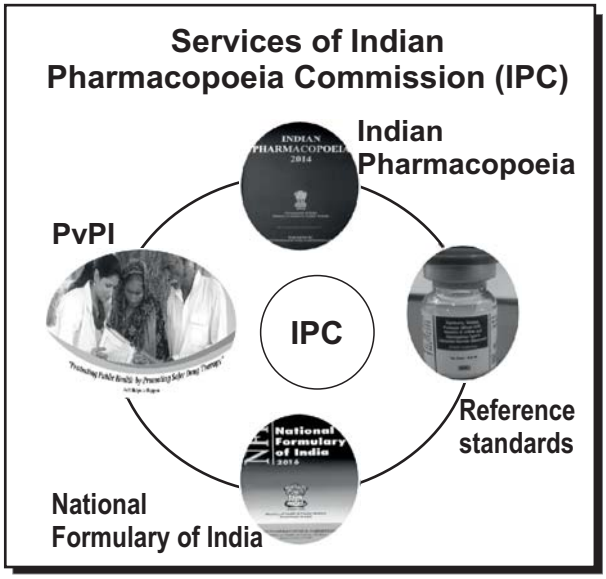
**R. Narayanaswamy**
Director - PKTI

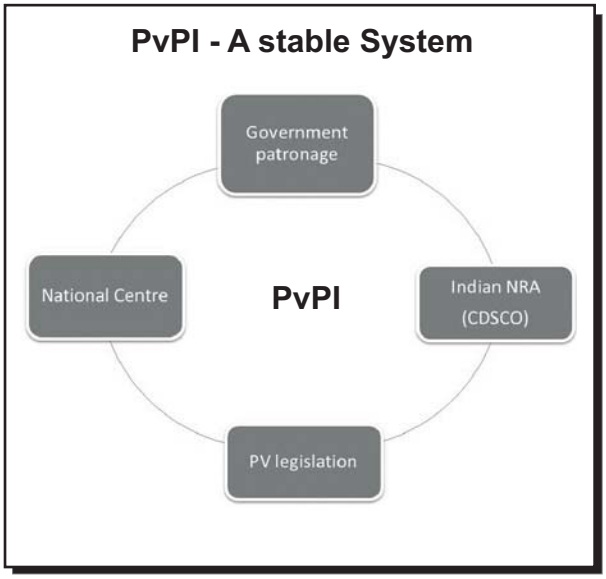
# ARTICLES

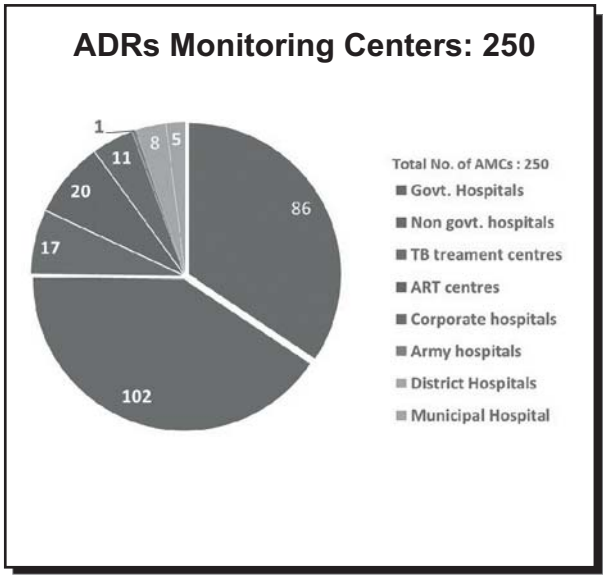
## PHARMACOVIGILANCE PROGRAMME OF INDIA (PVPI): *- REGULATORY IMPLICATIONS*

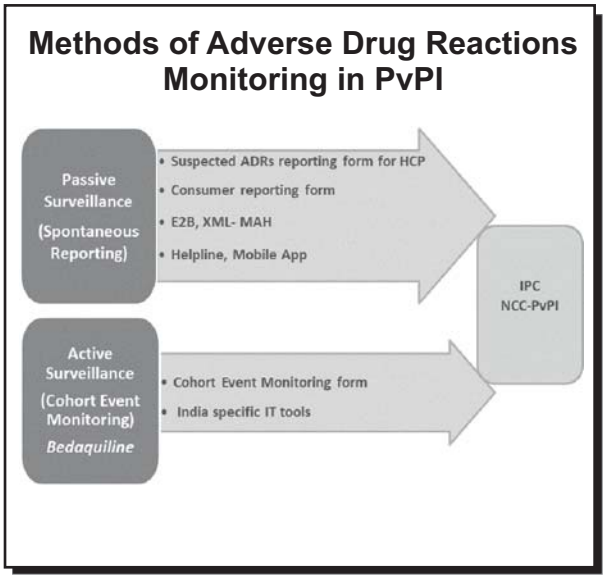
by

**Dr. V. Kalaiselvan,**
**Principal Scientific Officer, Indian Pharmacopoeia Commission, Ghaziabad,**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

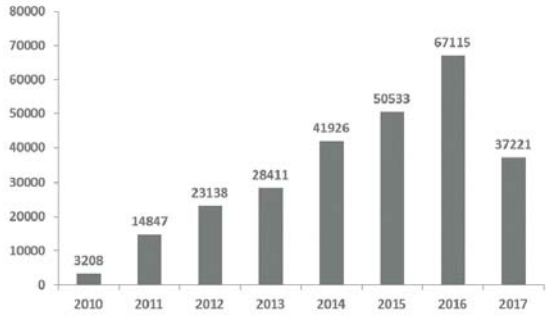


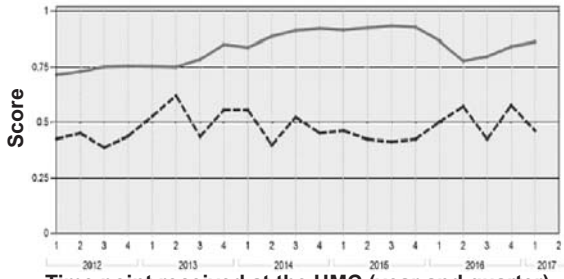
## Reporting Status




## ICSRs Completeness Score: India Vs Other Countries

**Average Completeness Score, India**

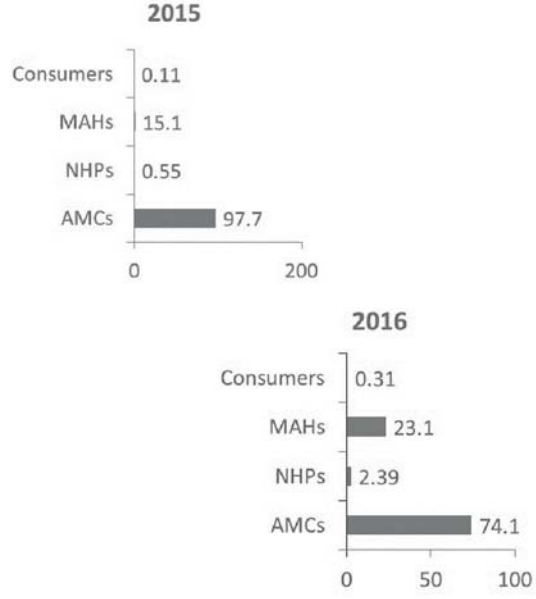
**Average Completeness Score over time**




**Time point received at the UMC (year and quarter)**

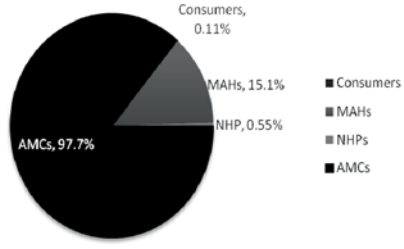
- - All countries — India

## ICSRs Reporting Status to NCC-PvPI by various stakeholders

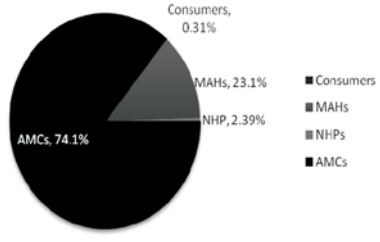



## ADRs Reporting Status to PvPI- 2015&2016

**ADRs Reporting Status to NCC-PvPI-2015**

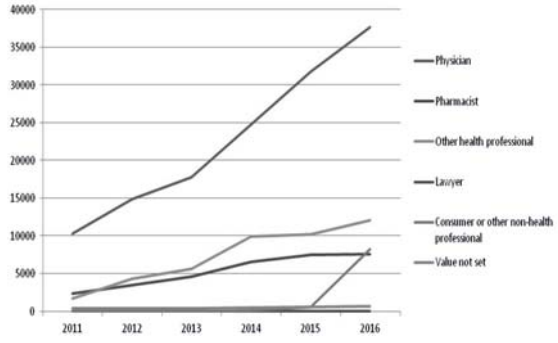



**ADRs Reporting Status to NCC-PvPI-2016**



## The Percentage of ADR reporting by various health care professionals and patients

Physician - 60%  Lawyer - 0.002%  Pharmacist - 14%
Other health professional - 19%  Value not set - 1.3%
Customer & Other non-health professional - 3.9%




## Pharmacists Role in PvPI

Regional Level
(Clinical oriented practice)

National Level
(Regulatory oriented practice)

**ADR**
a. Monitoring
b. Processing
c. Assessment
d. Reporting
d. Prevention

a. ICSRs/PSURs processing and quality review

b. Data mining Signal review

c. Benefit – risk assessment

d. Compliance to regulatory guidelines

REGD. NO. D. L.-33004/99

भारत का राजपत्र
The Gazette of India

EXTRAORDINARY
PART II—Section 3—Sub-section (i)
PUBLISHED BY AUTHORITY
NEW DELHI, TUESDAY, MARCH 8, 2016/ PHALGUNA 18, 1937

2. In the Drugs and Cosmetics Rules, 1945, in Schedule Y,-

(A) for paragraph "(2) **Post Marketing Surveillance**" and clause (i) relating thereto, as published in Part II, Section 3, Sub-section (i) of the Gazette of India, Notification G.S.R. 32 (E) dated 20th January, 2005, at page 63, the following shall be substituted, namely:-

"**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 drug 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.

## PSURs Office Memorandum

File. No 12-01/16-D-C (Pt-151)
Central drugs standard control organization
Directorate General of Health Services
FDA Bhavan, New delhi
(New Drugs Division)

Date: 23.11.2016

**Office Memorandum**

**Subject: Review/ Evaluation of PSURs data-reg.**

As per requirements of Schedule Y of Drugs and Cosmetics Rules, subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants are required to furnish Periodic Safety Update Reports (PSURs), every six months for the first two years after approval of drug is granted to the applicant, and annually for subsequent two years.

Evaluation of PSURs is a part of post marketing surveillance and overall pharmacovigilance activity and PvPI in IPC, the National Coordination Centre (NCC) is responsible for collection of spontaneous Adverse Drug Reactions (ADRs) from the ADR monitoring centres across the country and to collect, collate, analyse and identify new signals of any, for regulatory interventions by CDSCO, whenever necessary.

In view of above, it has been decided in consultation with the ministry that PSURs submitted by the marketing authorisation holders may be jointly evaluated by officials from CDSCO and PvPI at regular intervals and whenever required expert opinion may be taken from the subject experts. Finally, the divisional head of the said new drug (which is under evaluation with respect to PSUR) shall be responsible and may lead the collection, collation, analysis and final regulatory intervention/disposal of PSURs.

(Dr. G.N.Singh)
Drugs Controller General (I)

To

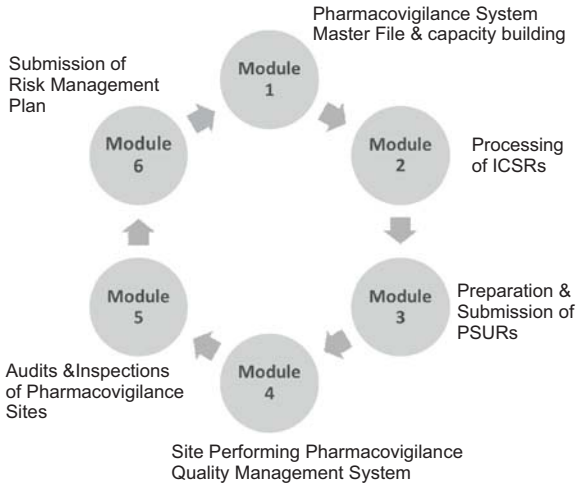
Pharmacovigilance Programme of India, IPC, Ghaziabad.

Copy to: PPS.
AS (F&D)
JS (R)

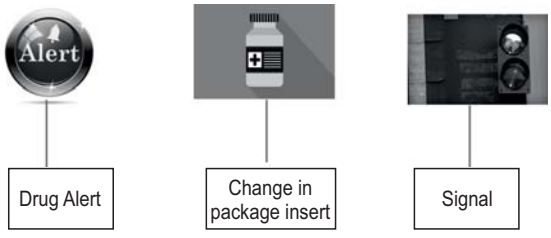
## Draft Pharmacovigilance Guidelines for Marketing Authorization Holders of Pharmaceutical Products in India

- Jointly Developed by PvPI and CDSCO for effective implementation of Pharmacovigilance in Pharmaceutical industries
- Ensuring good Pharmacovigilance practices
- These guidelines to be followed by Industries, PvPI and CDSCO

## Modules in the Guideline

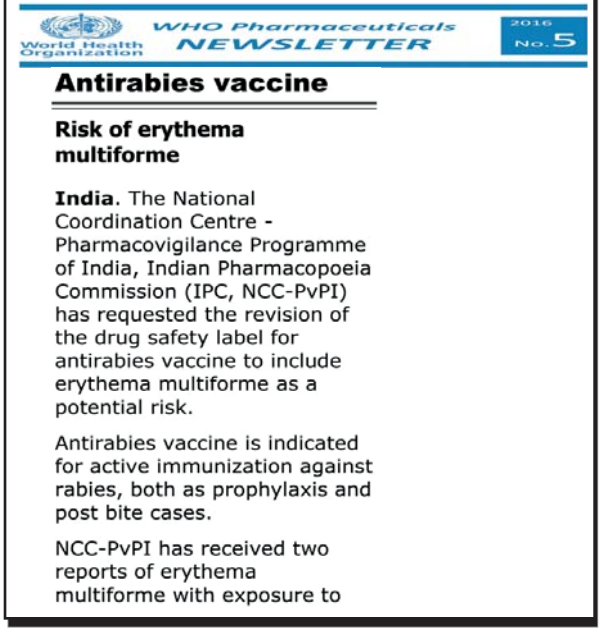



## Recommendations to Indian Regulatory Body




| Drug Alert | Change in label or package insert | Signal |
|---|---|---|
| 30 | 17 | 04 |

## Regulatory Matters Reflected in WHO Newsletter


World Health Organization WHO Pharmaceuticals NEWSLETTER 2016 No.5

### Antirabies vaccine

**Risk of erythema multiforme**

**India.** The National Coordination Centre - Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission (IPC, NCC-PvPI) has requested the revision of the drug safety label for antirabies vaccine to include erythema multiforme as a potential risk.

Antirabies vaccine is indicated for active immunization against rabies, both as prophylaxis and post bite cases.

NCC-PvPI has received two reports of erythema multiforme with exposure to

## Regulatory Matters Reflected in WHO Newsletter

World Health Organization — WHO Pharmaceuticals NEWSLETTER — 2016 No.5

### Azithromycin

**Risk of acute generalized exanthematous pustulosis**

**India**. The IPC, NCC-PvPI has requested the revision of the drug safety label for azithromycin to include exanthematous pustulosis as a potential risk.

Azithromycin is used in the treatment of mild to moderate susceptible infection including respiratory tract infections, uncomplicated skin /skin structure, non-gonococcal urethritis cervicitis.

NCC-PvPI has received five reports of exanthematous pustulosis with exposure to azithromycin between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC and the WHO Collaborating Centre for International Drug Monitoring (UMC).

## Regulatory Matters Reflected in WHO Newsletter

World Health Organization — WHO Pharmaceuticals NEWSLETTER — 2016 No.5

### Cefixime

**Risk of acute generalized exanthematous pustulosis**

**India**. The IPC, NCC-PvPI has requested the revision of the drug safety label for cefixime to include acute generalized exanthematous pustulosis as a potential risk.

Cefixime is used in the treatment of urinary tract infections, respiratory tract infections and billiary tract infections.

NCC-PvPI has received three reports of acute generalized exanthematous pustulosis with exposure to cefixime between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC.

***Reference:***
Based on the communication from IPC, NCC-PvPI, India *(www.ipc.gov.in)*

## MoU Between IPC and NABH

- Singed on 10th January 2017 for effective implementation of PvPI in corporate hospitals
- Mandatory for hospitals to report ADRs to PvPI for their NABH accreditation

## New Mobile App


- Developed by NCC-PvPI (in house)
- Administrative control at IPC
- Healthcare professionals and consumer reporting
- Attachment of source documents
- Attachment of Images of reaction
- XML generation

World Health Organization

*WHO Collaborating Centres*
*Global database*

Ref.No. [Initiator]
IND-145 [Headquarters]

Status
Active

Title of the centre:
**WHO Collaborating Centre for Parmacovigilance in Public Health Programmes and Regulatory Services**

Director / Head:
Dr GN Singh — dci@nic.in
Dr Vivekanandan Kalaiselvan — vivekarts@rediffmail.com

Institution:
Pharmacovigilance Division, Indian Pharmacopoeia Commission
Ministry of Health and Family Welfare

Address:
Sector 23, Raj Nagar
201 002
Uttar Pradesh

| Town: | Country: | Region: |
|---|---|---|
| Ghaziabad | INDIA | SEARO |
| Phone: | Fax: | Web Site: |
| +91 120 6582849 | | http://www.ipc.gov.in/PvPI/pv_home.html |
| Date of Designation: | Last Redesignation: | Expiry: |
| 18/Jul/2017 | 18/Jul/2017 | 18/Jul/2021 |

Terms of Reference:
1. Support WHO to develop relevant tools and guidelines for enhancing Pharmacovigilance (PV) practice in low and middle income countries (LMIC) in Asia and beyond.
2. Contribute to capacity building of WHO member states to establish high quality pharmacovigilance systems for medical products.
3. Scientific support to countries for pharmacovigilance in public health programmes (e.g. Tuberculosis, Neglected Tropical Diseases, Vector Borne Diseases, HIV-AIDS; Immunization Programme) and regulatory issues.
4. Work-sharing and joint activities in regulatory pharmacovigilance

Subjects:
1. Pharmaceuticals (including essential drugs and medicines)
2. Health systems research & development

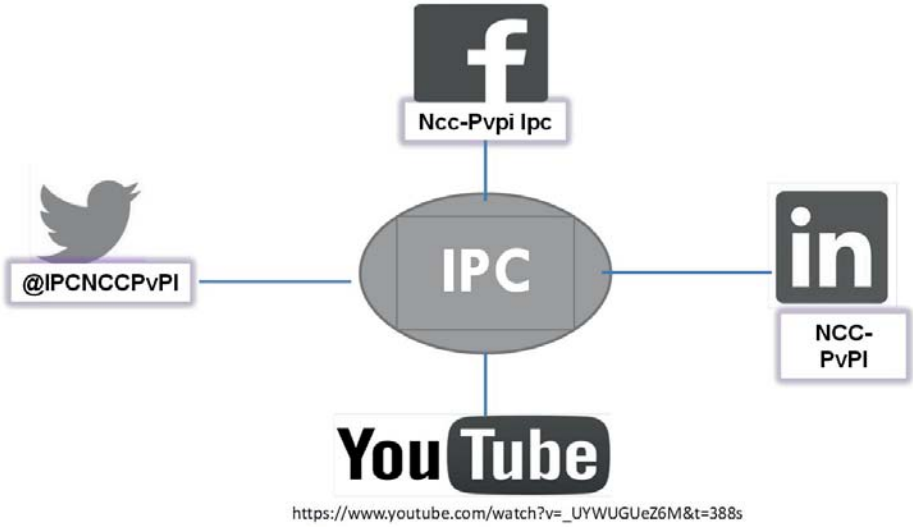
Types of activity:
1. Training and education
2. Development and application of appropriate technology
3. Providing technical advise to WHO

WHO Outputs:
4.3.3 - Improved quality and safety of medicines and other health technologies through norms, standards and guidelines, strengthening of regulatory systems, and prequalification

| Responsible Officer: | Phone: | Email: |
|---|---|---|
| PAL Shanthi Narayan | +41 22 791 1318 | pals@who.int |
| Technical Counterpart: | Phone: | Email: |
| GUPTA Madhur | +911142595600 | guptamadh@who.int |

Access to annual progress reports and the current workplan (this is accessible to WHO Staff Members only):
Link to eWork


# Join with us



# ROLE OF CDSCO IN PHARMACOVIGILANCE

by

**Dr. S. Manivannan,**
**Deputy Drugs Controller (India), CDSCO, South Zone, Chennai ,**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Overview of Pharmacovigilance

***Pharmacovigilance***

Science and activities related to detection, assessment, understanding and prevention of ADRs and other drug related problems

## History

- 1962 - USA – amendment to Federal Food Drug & Cosmetic Act
- 1964 – UK – Yellow card system
- 1968 – WHO – Program for International Drug monitoring
- 2000's- developing countries followed suit

## WHY ADR REPORTING IS NEEDED?

- Medicines safety is established in limited number of patients in clinical trials
- Less than 5000 human subjects are involved in clinical trials which allows to detect only common ADR
- Need to establish safety of medicines in special population that is children, elderly & pregnant women
- Even one ADR of a medicine in 10,000 population is considered as unsafe

## What to Report?

- PvPI encourages reporting of all types of suspected Adverse Reactions with all pharmaceutical products irrespective of whether they are known or unknown, serious or non serious and frequent or rare.
- Centers can capture all kinds of drug-related problems

## ADRs Reporting Forms

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

CDSCO

Central Drugs Standard Control Organization

Directorate General of Health Services,

Ministry of Health & Family Welfare, Government of India,

Nirman Bhawan, New Delhi - 110011

www.cdsco.nic.in

For VOLUNTARY reporting of Adverse Drug Reactions by health care professionals

Report#

To be filled in by Pharmacovigilance centres receiving the form.

A. Patient Information

1. Patient identifier (initials or In confidence)

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, including 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-yy): ____ ☐ Congenital anomaly

☐ Life threatening ☐ Required intervention to prevent permanent impairment/ damage

☐ Hospitalization-initial or prolonged ☐ Other (specify): ____

☐ Disability

15. Outcome

☐ Fatal ☐ Recovering ☐ Unknown

☐ Continuing ☐ Recovered ☐ Other (specify): ____

C. Suspected medication(s)

| Sl. 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 unknown, give duration) | | Reason for Use or prescribed for |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Date started | Date stopped | |
| i | | | | | | | | | | |
| ii | | | | | | | | | | |
| iii | | | | | | | | | | |
| iv | | | | | | | | | | |

9. No. As per C

9. Reaction abated after drug stopped or dose reduced: Yes / No / Unknown / NA / Reduced dose

10. Reaction reappeared after re-introduction: Yes / No / Unknown / NA / Re-introduced, dose

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

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address: ____

Pin code: ____ E-mail: ____

Cell No. / Tel. No. with STD Code: ____

Specialty: ____ Signature:

17. Occupation: ____ 18. Date of this report (dd-mm-yyyy):

## ADRs Reporting Forms

MEDICINES SIDE EFFECT REPORTING FORM (FOR CONSUMERS)

Version 1.0

Indian Pharmacopoeia Commission, National Coordination Centre- Pharmacovigilance Programme of India, Ministry of Health & Family Welfare, Government of India.

IPC

This reporting is voluntary, has no legal implication and aims to improve patient safety. Your active participation is valuable.

1.Patient Details

Patient Initials: ☐☐☐ Gender (√): Male ☐ Female ☐ Other ☐ Age (Year or Month) :

2. Health Information

a. Reason(s) for taking medicine(s)/(Disease/Symptoms):

b. Medicines Advised by (√): Doctor ☐ Pharmacist ☐ Friends/Relatives ☐ Self (Past disease experienced/No past disease experienced) ☐

3. Details of Person Reporting the Side Effect

Name (Optional):

Address:

Telephone No: Email:

4. Details of Medicine Taking/Taken

| Name of Medicines | Quantity of Medicines taken (e.g. 250 mg, Two times a day ) | Expiry Date of Medicines | Date of Start of Medicines | Date of Stop of Medicines |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

Dosage form (√) : Tablet ☐ Capsule ☐ Injection ☐ Oral Liquids ☐ If Others (Please Specify.....)

5. About the Side Effect

When did the side effect started? Side Effect Continuing ( Yes/No):

When did the side effect stopped?

6.How bad was the Side Effect? (Please √ the boxes that Apply)

☐ Did not affect daily activities ☐ Affect daily activities

☐ Admitted to hospital ☐ Death

☐ Others

7.Describe the Side Effect (What did you do to manage the side effect?)

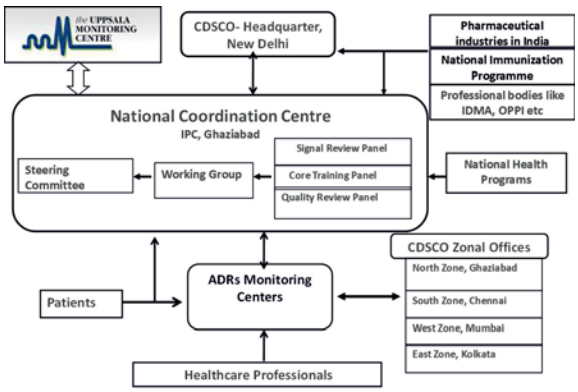
The information provided in this form will be forwarded to ADR Monitoring Centre for followup. You are requested to cooperate with the programme officials when they contact you for more details. Please do report if you do not have all the information

Please turn the page to read the instructions

## Pharmacovigilance Programme of India

- Ministry of Health & Family Welfare, Government of India has initiated a nation-wide Pharmacovigilance Programme for protecting the health of the patients by assuring drug safety in the year 2010
- Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Government of India, is functioning as NCC for PvPI since 15th April 2011

## PvPI Communication



## Objectives

- To create a nation-wide system for patient safety reporting
- To identify and analyse the new signal (adr) from the reported cases
- To analyse the benefit - risk ratio of marketed medications
- To generate the evidence based information on safety of medicines
- To support regulatory agencies in the decision-making process on use of medications
- To communicate the safety information on use of medicines to various stakeholders to minimise the risk
- To emerge as a national centre of excellence for pharmacovigilance activities
- To collaborate with other national centres for the exchange of information and data management
- To provide training and consultancy support to other national pharmacovigilance centres located across global

## Who can report ADRs?

- All healthcare professionals (clinicians, dentist, pharmacists, nurses)
- Non healthcare professionals (lawyers, Patients, consumers etc) can report ADRs
- Submission of an ADR report does not have any legal implication on the reporter

## Role of CDSCO in implementation of PvPI

### GSR 287 (E) DATED 08.03.2016 - DRUGS & COSMETICS (FIRST AMENDMENT) RULES 2016

**Post Marketing Surveillance**

In Schedule "Y" of Drugs and Cosmetics Rules, 1945 the following shall be substituted

**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 drug 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.";

## PvPI Recommendations to CDSCO for Regulatory Actions

| S.No | Suspected drugs | Adverse drug reactions | Recommendations | Action taken by CDSCO |
|---|---|---|---|---|
| 1 | Carbamazepine | Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) | For Drug Safety Label Change – Patient may be screened for HLA-B*1502 prior to initiating the carbamazepine treatment | Issued an order to all MAHs to comply the same |
| 2 | Mannitol | Hypokalaemia | To include in Prescribing Information | In process |
| 3 | Piperacillin and Tazobactam | Hypokalaemia, Bronchospasm | To include in Prescribing Information | Issued an order to all MAHs to comply the same |
| 4 | Rota Vaccine | Intussusception | To include in Prescribing Information | In process |
| 5 | Ranitidine | Cardiac Arrest | To include in Prescribing Information | In process |
| 6 | Anti-Rabies Vaccine | Erythema Multiforme | To include in Prescribing Information | Issued an order to all MAHs to comply the same |
| 7 | Pulmonary Surfactant | Pulmonary Haemorrhage | To include in Prescribing Information | In process |
| 8 | Ceftriaxone | Stevens Johnson syndrome | To include in Prescribing Information | In process |
| 9 | Lamotrigine | Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) | To include in Prescribing Information | In process |
| 10 | Betamethasone | Photosensitivity Reaction | To include in Prescribing Information | In process |

## PvPI Recommendations to CDSCO for Regulatory Actions

| S.No | Suspected drugs | Adverse drug reactions | Recommendations | Action taken by CDSCO |
|---|---|---|---|---|
| 11 | Azithromycin | Acute Generalised Exanthematosus Pustulosis (AGEP) | To include in Prescribing Information | In process |
| 12 | Cloxacillin | Acute Generalised Exanthematosus Pustulosis (AGEP) | To include in Prescribing Information | In process |
| 13 | Cefixime | Acute Generalised Exanthematosus Pustulosis (AGEP) | Signal | In process |
| 14 | Itraconazole | Photosensitivity reaction | To include in Prescribing Information | In process |
| 15 | Ibuprofen | Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) | To include in Prescribing Information | In process |
| 16 | Amoxicillin/ Clavulanate Potassium | Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) | To include in Prescribing Information | In process |
| 17 | Ciprofloxacin | Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) | To include in Prescribing Information | In process |
| 18 | Sodium Valproate | Gum Hyperplasia | To include in Prescribing Information | In process |
| 19 | BCG vaccine | Lymphadenopathy | To include in Prescribing Information | In process |
| 20 | Docetaxel | Candidiasis | To include in Prescribing Information | In process |
| 21 | Furosemide | Dermatitis Lichenoid | Signal | SEC of CDSCO approved the same |
| 22 | Itraconazole | Acute Generalised Exanthematosus Pustulosis (AGEP) | Signal | In process |
| 23 | Lithium Carbonate | Drug Reaction with Eosinophilia and Systemic symptoms Syndrome (DRESS) | Signal | SEC of CDSCO approved the same |
| 24 | Phenytoin | Acute Generalised Exanthematosus Pustulosis (AGEP) | To include in Prescribing Information | SEC of CDSCO approved the same |

## Role of CDSCO Zonal Offices in Effective Implementation of PvPI

### GENERAL

- Visiting to AMCs to ensure best pharmacovigilance practices
- Random verification of Individual Case Safety Reports and its respective source documents at AMCs
- Taking necessary action in coordination with state regulatory authority on a particular product - in case of adverse events encountered

## TECHNICAL SUPPORT

- Monitor and report ADRs
- Participating as Faculties in raining and workshops

### LOGISTICS AND ADMINISTRATIVE SUPPORT

- Bridging the gap between ADRs monitoring centers (AMCs) and National Coordination Centre
- Facilitating manpower appointment and developing infrastructure at AMCs

# INTRODUCTION AND OBJECTIVES OF PHARMACOVIGILANCE

by

**Dr. G. Parthasarathi,**
**Dean, Global Engagement, Professor, Pharmacy Practice, JSS University, Mysuru,**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Pharmacovigilance

- Pharmacovigilance is concerned with the development of science and regulation in the area of drug safety
- Pharmacovigilance aims at
  - the detection, assessment and prevention of adverse effects and other problems related to the use of medicines

## Why Pharmacovigilance?

- Humanitarian concerns
- Economic concerns

## Why Pharmacovigilance?

- Safety information collected during drug development is incomplete:
  - Clinical trials evaluate limited duration and limited numbers of carefully selected patients in carefully selected settings
- Information often incomplete or not available on:
  - Rare but serious reactions
  - Use in vulnerable groups (pregnancy, children)
  - Persons with multiple diseases/conditions
  - Risk of long-term and/or repeated use

## Merit assessment

- Worth of a Medicine is in a given context
  - Medicines will always do good to us
  - Medicines are chemicals foreign to our body and hence are always dangerous
  - Medicines are intended for doing good (treatment) but can be harmful at times

## Merit assessment

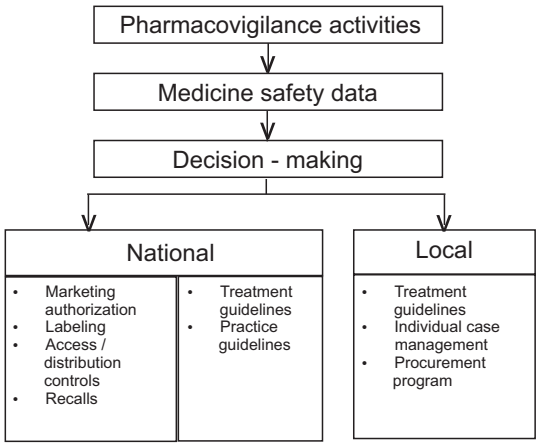
## Safety Requirements

- No drug is absolutely safe
- "Safety" = benefits exceed risks for defined population and use
- Determination of safety is inseparable from consideration of the drug's effectiveness; benefit-risk and can change over time.

## Scope of Pharmacovigilance

- **Adverse effects** (properties of ingredients or patient)
- Patient effects of **inadequate** product **quality** (failing GMP, distribution, storage, counterfeiting etc.)
  e.g. unexpected lack of efficacy
- Patient effects of inadequate use
  - medication errors
  - dependence and abuse
  - antibiotic resistence
  - poisoning

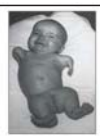
## Use of Pharmacovigilance




## Ultimate Goals of Pharmacovigilance

- The rational and safe use of medicinal products
- The assessment and communication of the risks and benefits of drugs on the market
- Educating and informing of patients

## How it Started?



1961
Thalidomide

1968
WHO creates Programme for International Drug Monitoring

1978
Swedish Government and WHO creates UMC and Collaborating Centre

## Aim of the WHO PV Programme

To ensure that early signs of previously unknown medicine-related safety problems would be identified and information about them shared and acted upon

The Global Fund

World Health Organization

**Minimum Requirements for a functional Pharmacovigilance System**

**Introduction**

Pharmacovigilance (PV) is defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems"[1]. It is a very important medical discipline to prevent drug-related adverse effects in humans, ensure patient safety and promote the rational use of drugs.

PV is well established in most industrialized countries but its practice in low and middle income countries is variable with some countries having absolutely no systems at all whilst a few have systems comparable to the best in industrialized countries. In view of the importance of pharmacovigilance to all countries, the World Health Organisation, upon request from the Global Fund against AIDS, TB and Malaria (Global Fund) and key multilateral and technical agencies, has embarked upon an extensive and wide ranging consultative process to produce a Pharmacovigilance Strategy for use by all countries that are seeking to advance PV systems, through the Global Fund and similar health initiatives. The process includes the identification of (and the specifications for) the minimum requirements for PV.

http://www.who.int/medicines/areas/quality_safety/safety_efficacy/saf_pub/en/

## WHO Drug Monitoring Programme
**Founding Members 1968**

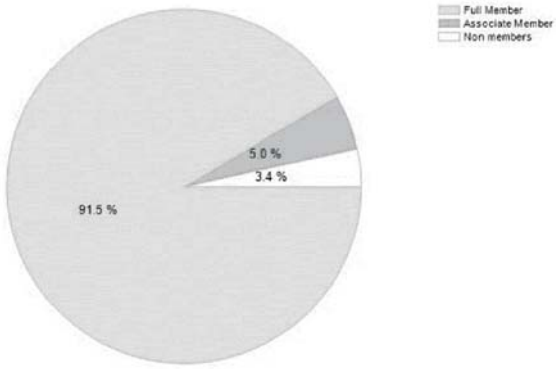
## WHO Drug Monitoring Programme
## Member Countries
**January 2017**

https://www.who-umc.org/

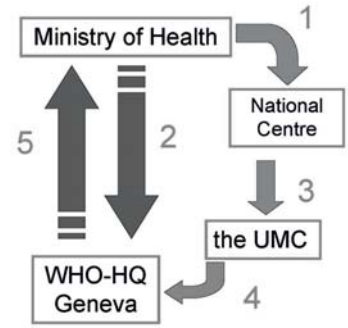
## Population Coverage

January 2017

Proportion of global population covered by WHO pharmacovigilance network




## Process for joining WHO Programme

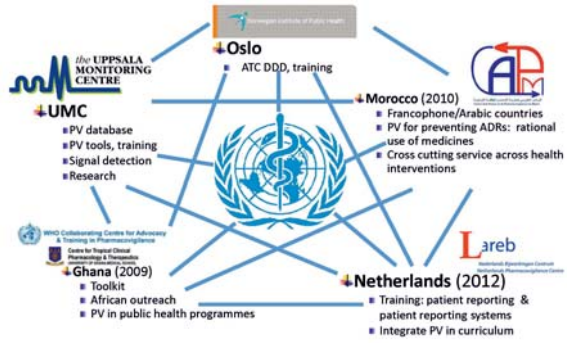



**1.**Ministry of Health (or equivalent) designates National Centre
2.Ministry of Health sends formal application to WHO-HQ, Geneva
3.National Centre sends sample reports to the UMC
4. UMC notifies WHO-HQ that reports are compatible
5. WHO-HQ advises Ministry of Health of admittance to the Programme

## Pharmacovigilance in WHO

- Establish PV systems and centres in every country in the world.
- Maintain the network of PV centres worldwide.
- Provide a platform for data sharing and exchange of information.
- Develop methods, norms and standards for PV in LMIC, PHPs.
- Bring capacity, resources.
- Provide 'PV service' to all programmes that use medicinal products in WHO.

## WHO Collaborating Centres for PV




## UMC/WHO Guidelines (2000)


**Available in:**

English
Spanish
French
Russian
Italian
Korean
Portuguese

## WHO Handbooks malaria, HIV/AIDS, TB vaccines 2006 - 2014

## PV guidelines


## Pharmacovigilance Programme of India (PvPI)

- July 2010 - CDSCO, New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide pharmacovigilance programme (PvPI)
- All India Institute of Medical Sciences (AIIMS), New Delhi was the National Coordinating Centre (NCC)
- 22 ADR monitoring centres (AMCs) including AIIMS, New Delhi had been set up under this Programme
- April, 2011 – NCC shifted from AIIMs to Indian Pharmacopoeia Commission (IPC), Ghaziabad
- Currently there are 250 AMCs throughout India

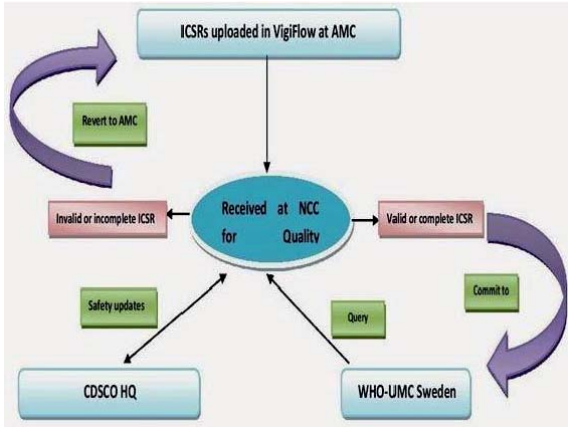
## Vision and Mission of PvPI

- The vision of PvPI is to improve patient safety and welfare in Indian population by monitoring drug safety and thereby reducing the risk associated with use of medicines

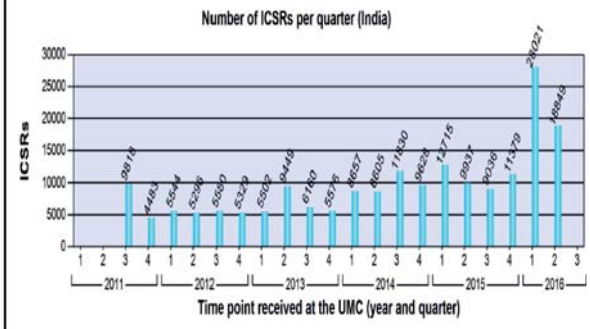
- The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of use of medicine outweighs the risks associated with its use

## Partners of PvPI

## Monitoring of ADRs through PvPI




## India's Contribution to WHO-UMC



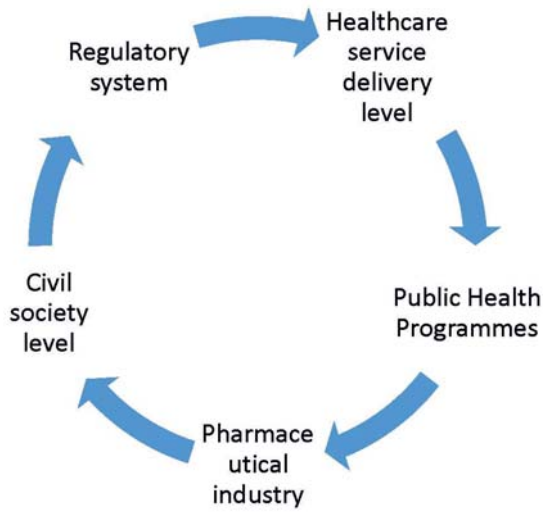

## PvPI Recommendations

**PvPI recommendations and Regulatory actions**

PvPI, Signal Review Panel Recommendations to CDSCO from the year 2014-15.

| S No. | Drugs : Adverse Drug Reactions | Recommendations | Action Taken |
|---|---|---|---|
| 1 | Carbamazepine : Steven Johnson Syndrome/Toxic Epidermal Necrolysis | Label change – Patient may be screened for HLA-B* 1502 prior to initiating the Carbamazepine treatment | CDSCO instructed Marketing Authorization Holders (MAH) to comply the same |
| 2 | Pazopanib HCL : Cardiac dysfunction / Heart attack | Advisory Note | Recommended to CDSCO |
| 3 | Sunitinib HCL : Hepatobiliary disorder, Cardiovascular dysfunctions , Haemorrhage/ Bleeding disorder | Advisory Note | Recommended to CDSCO |
| 4 | Mannitol : Hypokalaemia | For Label change | Approved in the Subject Expert Committee (SEC) of CDSCO. |
| 5 | Rotavirus Vaccine : Intussusception | For Label change | Approved in the SEC of CDSCO. |
| 6 | Piperacillin & Tazobactam : Hypokalaemia, Bronchospasm | For Label change | Approved in the SEC of CDSCO. |
| 7 | Ranitidine : Cardiac Arrest | For Label change | Recommended to CDSCO |
| 8 | Anti Rabies Vaccine : Erythema Multiforme | For Label change | Recommended to CDSCO |
| 9 | Surfactant : Pulmonary Haemorrhage | For Label change | Recommended to CDSCO |
| 10 | Lamotrigine : Stevens Johnson Syndrome, Toxic Epidermal Necrolysis | For Label change | Recommended to CDSCO |
| 11 | Ceftriaxone : Stevens Johnson Syndrome | For Label change | Recommended to CDSCO |
| 12 | Betamethasone : Photosensitivity Reaction | For Label change | Recommended to CDSCO |
| 13 | Azithromycin : Acute generalized exanthematous pustulosis | For Label change | Recommended to CDSCO |
| 14 | Cloxacillin : Acute generalized exanthematous pustulosis | For Label change | Recommended to CDSCO |

## A complete PV system



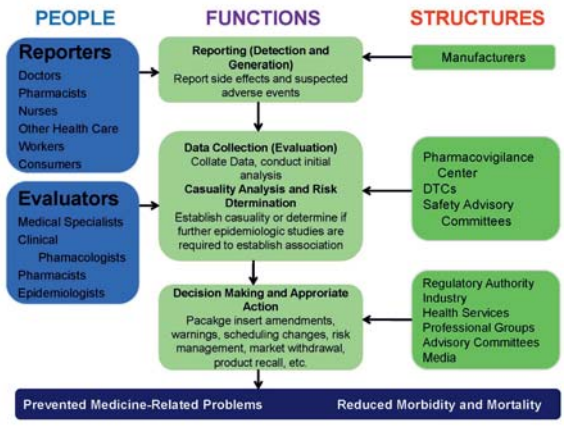

We need to build competence at all levels

## A complete PV system

- Governance, policy, laws & regulations, budget
- Structures, processes, stakeholder coordination
- Data management & signal analysis
- Risk assessment & evaluation
- Risk management & communication

## Stakeholders

- Drug regulatory authority
- Healthcare professionals
- Public health programmes
- Pharmaceutical companies
- Media
- Academic institutions
- Professional associations
- Consumer and patient organizations
- Pharmacovigilance centres in other countries




## Structure

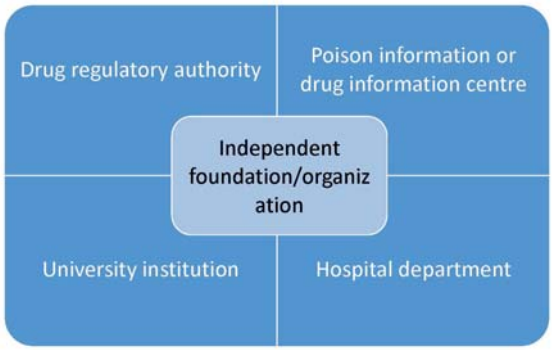

**Centralized**

Regional centre


**Decentralized**

## Organization

Options for Affiliation of national center




## Resources

**Technical**

- computer with printer and scanner
  - standard office software
  - report management system
    - complying with int. standard eg. VigiFlow
- Literature sources
- Internet access, e-mail, telephone, fax

## Resources

**Human**

- Pharmaceutical competence
- Medical competence
- Administrative assistance
  - dedication
  - education
- Formal training
- Visit country with functional system

## PV at Healthcare Delivery

- Explain to colleagues why, what and how they need to report
- Common perception that ADRs and ME don't happen in our facility
- ~ 5% hospital admissions due to ADRs
- Those who do not find them are not looking
- Without documenting and reporting we will never learn and improve

## PV at Service Delivery Level

**High-quality systems:**

- Encourage reporting of ADRs, errors and unexpected lack of effect
- Are non-punitive
- Analyse underlying reasons (root-cause)
- Learn from mistakes
- Provides feed-back for continues improvement of practices
- Prevent harm to future patients


## PV in Public Health Programmes

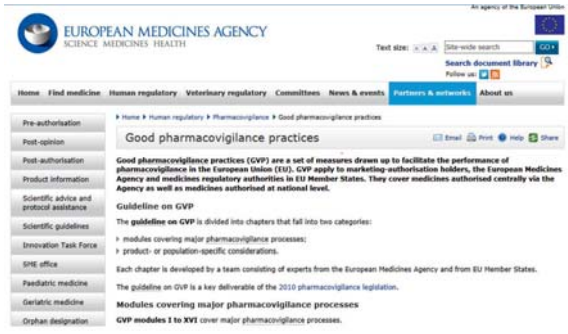
PHP managers have a different mindset

- Ensure successful implementation of programme
- **Minimize threats** to confidence in programme e.g adverse reactions & errors

Spontaneous reporting not good enough for PHP managers

- **Active monitoring** to identify magnitude of risk and incidence of most serious reactions


## PV in the Pharmaceutical Industry




### Requirements by National Regulatory Authority (NRA)

**Marketing Authorisation Holders (MAH) must**

- Have a Qualified Person for PV (QPPV)
- Submit adverse events from clinical trials
- Submit PV and/or Risk Management Plans
- Spontaneously reported ADR (serious within 15 days)
- ADR reports from Post Authorisation Studies (PASS)
- Periodic Update Safety Reports (PSUR/PBRER)

### Empowering the public

## PV at the Civil Society Level

- **Involvement of consumer organizations**
  - **Mobilization against substandard medicines**

*International Journal of Business and Management Invention*
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*www.ijbmi.org Volume 3 Issue 1\ January. 2014\ PP.14-21*

**Evaluating Consumers' Protective Measures Against Unethical Marketing Of Medical Drugs In Nigeria**

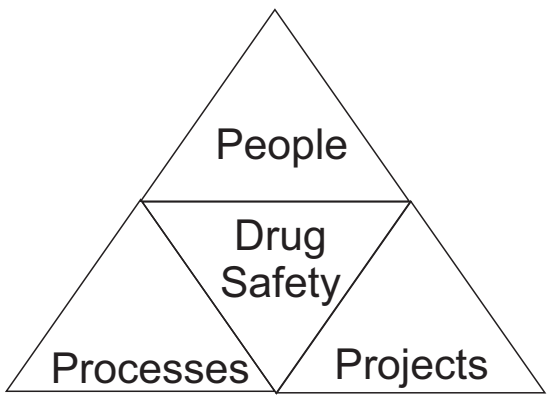
Onwubiko N.Dike[1], Julius O. Onah[2]
*1. Department of Management Sciences, Rhema University, PMB 7021, Aba, Abia State, Nigeria*
*2. Department of Marketing, University of Nigeria, Nsukka, Enugu State, Nigeria.*

***ABSTRACT:*** *The study appraised the measures adopted by consumers to protect themselves against the unethical marketing of medical drugs in Nigeria, particularly the South Eastern States. The study was a survey design. Stratified, simple random, convenience and judgmental sampling procedures were adopted. One research question and a hypothesis guided the study. The target population was 5621 respondents, involving 3444 healthcare professionals, (doctors, pharmacists, nurses), 1641 drug consumers, 390 licensed drug firms and 146 senior staff of the regulatory agencies in Abia, Anambra, Ebonyi, Enugu and Imo States. Five University Teaching Hospitals constituted the study canters. A sample of 985respondents was derived. Primary and secondary sources of data were accessed. Pilot study was conducted. The research instrument was validated and the reliability estimated using Cronbach's Alpha technique. The reliability coefficient was 0.971; indicating high degree of internal consistency of the instrument .The mean (x) and criterion mean scores were used to answer the research question. Z-test statistical technique was applied in testing the hypothesis at 0.05 level of significance and 4 degrees of freedom. The findings revealed that consumers do not significantly adopt measures to shield themselves from counterfeit medications. Recommendations were made.*

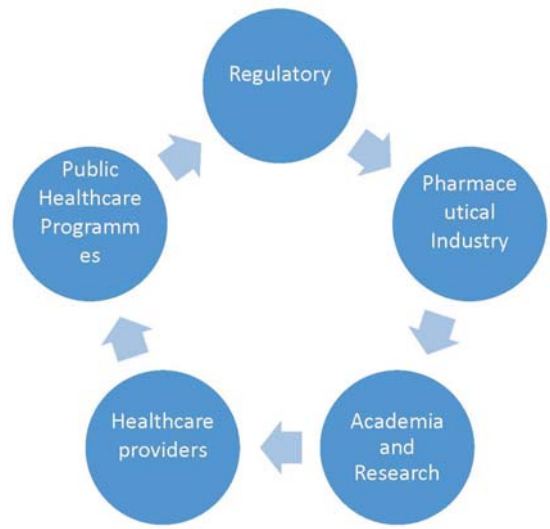
***KEYWORDS:*** *Protective Measures, Unethical Marketing, Medical Drugs, Drug Consumers, Counterfeit Medications.*

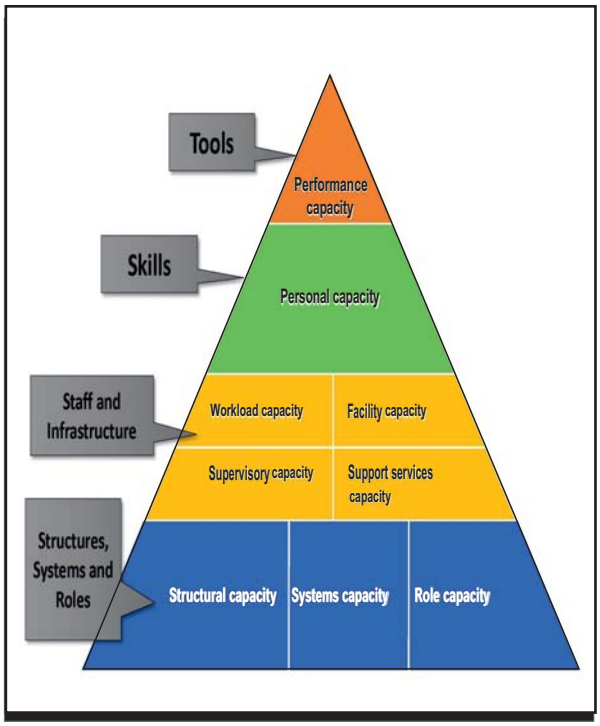
## Capacity Building


## Capacity Building - The Key




## Capacity Building






**Summary**

**Functions of a PV system**

- Data Collection
- Data Management
- Signal detection
- Safety issue assessment
- Decision - making
- Action and Communication
- Follow-up

# ESTABLISHING PHARMACOIVILANCE PROGRAMME IN HOSPITALS

by

**Dr. G. Parthasarathi,**
**Dean, Global Engagement, Professor, Pharmacy Practice, JSS University, Mysuru,**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## What is Pharmacovigilance ?

The science and activities relating to
- detection, assessment, understanding, prevention of adverse effects or any other medicine-related problem

- **Scope includes**
  - SSFFC (spurious, substandard, falsely labeled, falsified,
  - counterfeit medicines)
  - Antimicrobial resistance
  - Medication errors
  - Misuse

## Hospital based PV centre .....

- Can contribute greatly in generating the safety data

- Operates through its PMS /holistic / comprehensive approach

## Establishing Hospital Based Pharmacovigilance Centre

- New centre can start operating very quickly
- But from uncertain stage to becoming an established and effective organisation .....
  - time, vision, dedication, expertise and continuity

## Basic Requirements

Effective functioning of PV centre depends
- Staff
- Infrastructure
- Funding

## Establishing ADR Monitoring Programme in Hospital

**Staff requirements**
- Full time / part-time (initial)
- Minimum / essential qualification
  - Basic qualification - MBBS/ PharmD/ BDS
  - Desirable
    - Postgraduate qualification
    - Expertise in clinical medicine, pharmacology, toxicology & epidemiology
    - Experience / trained personnel
    - Communication skills
    - Committed and dedicated

## Establishing ADR Monitoring Programme in Hospital

**Staff requirements**

- Adequate staff
  - Size of the centre
  - Assessment time / case report (I hour)
- Secretarial assistance

Take care of the education of pharmacovigilance staff regarding:

- Data collection and verification
- Interpreting and coding of adverse reaction descriptions
- Coding of drugs
- Case causality assessment
- Signal detection
- Risk management

## Establishing ADR Monitoring Programme in Hospital

- **Infrastructure**
- **Location**
  - Any department in a hospital
  - Ideal : clinical pharmacy / clinical pharmacology / clinical toxicology / epidemiology
- **Space**
  - Adequate to house staff & infrastructural requirements
- **Communication system**
  - computer, internet connection
  - telephone and fax
  - printer, photocopier

## Establishing ADR Monitoring Programme in Hospital

- **Information system**
  - standard texts and references,
  - literature sources related to ADRs
  - hospital library (teaching hospital)
- **Office equipment**
  - computer chair and table
  - office table and chair
  - cup boards /
  - book shelves and journal rack
- Adequate ventilation and lighting

## Initiation Process

- Create awareness amongst HCPs
  - Seminars, workshops, personal & training meets
- Adopt suitable and feasible method
  - Spontaneous reporting system
- Design ADR reporting & documentation forms
  - Simple yet comprehensive
- Ensure easy access to reporting forms
- Assist HCPs in identifying the event & provide updates on drug safety issues

## Initiation Process...

- Provide feedback on the reported information
  - 'Thank you' notes
- Develop a suitable database
  - for easy documentation & retrieval of information
- Communicate and disseminate the information
- Have a contacts with international institutions working in pharmacovigilance
  - WHO Department of Essential Drugs and Medicines Policy
  - Uppsala Monitoring Centre, Sweden

## Sustaining the Process

- Design and distribute campaigning materials relating to importance of pharmacovigilance
- Conduct continuing education programmes for health care professionals
- Promote the importance of reporting of adverse drug reactions through professional publications, and communication activities

## Reporting of ADRs

- Spontaneous reporting is the back bone of pharmacovigilance system
- **Reporting form**
  A notification relating to a patient with an adverse medical event suspected to be induced by a medicine
- Electronic reporting

## Reporting Form – Essentials

- Patient Information: age, sex and brief medical history
- Adverse event: description, start date, course and outcome, any relevant data by lab investigations
- Suspected drug(s) information: name, brand, manufacturer details, dose, route, start/stop dates, indication for use
- Details of concomitant drugs
- Risk factors if any (impaired renal function, previous exposure to suspected drug, previous allergies, social drug use)
- Details of the Reporter

## Who can Report ?

- Medical practitioners
- Pharmacists
- Dentists
- Nursing staff
- Interns and PGs

## What to Report ?

- All suspected adverse reactions - known or not, serious or not
- Serious and or life threatening reactions
- Fatal reactions
- Reactions resulted in disabilities or permanent harm
- Reactions resulted in increased healthcare costs

## What to Report ?

- Severe reactions of any type
- Any reactions to newer drugs
- Newer reactions to any drugs in the market
- Rare and uncommon adverse reactions

## Under Reporting

- Common phenomenon – technical and psychological issue
- Lack of knowledge / understanding regarding the system
- Fear of negative competence / litigation
- Underestimation of the true size of a problem

## How to Stimulate Reporting ?

- Easy access to reporting forms and other means of reporting
- Acknowledging the receipt of ADR reports by personal letter or phone call
- Providing feedback to reporters in the form of articles in journals, adverse drug reaction bulletins or newsletters
- Participation of the centres staff in UG and PG education and scientific meetings
- Collaboration with local drug or pharmacovigilance committees / professionals associations

## Assessment of Case Reports

- Quality of documentation
- Coding of drugs (WHO ATC), adverse events (WHO ART)
- Relevance of reaction
- Identification of duplicate reports
- Causality assessment

## ADR Assessment Committee

- A multi disciplinary advisory committee is desirable, to support the PV centre with regard to the quality of the procedures in:
  - Data collection and assessment
  - Interpretation of the data
  - Publication of information

## Use of the data

Data collected in pharmacovigilance can be used in a variety of ways

- Hypothesis generation and strengthening
- Drug regulation
- Information (dissemination)
- Education and feedback
- Limitations regarding the use of the data

## Relations with other parties

- The Drug Regulatory Authority
- Pharmaceutical companies
- Professional medical and pharmaceutical associations
- National pharmacovigilance centers
- WHO Collaborating Centre for International Drug Monitoring
- Academia
- Media and consumer organizations

## Funding

- A pharmacovigilance centre should have some basic, regular source of funding (in order to ensure continuity in its work)
- Requires adequate funding to meet the expenses:
  - Recurring cost
  - Non recurring cost
  - Maintenance cost
- Cost estimation:
  calculated as a function of the rate of reporting required and the size of the population

## Funding

**Basic sources**

- university departments
- professional associations
- governmental departments (National centre/projects)
- non governmental organisation (with an interest in drug safety).
- health insurance companies and health insurance funds

## Funding

**Cost can be minimized**

- By starting the PV service in poison control and drug information centres
- have much in common with pharmacovigilance centres, both in organisation and from a scientific point of view.
- Expensive facilities such as secretariat, computer resources and library services can be shared.
- In any case close collaboration between these organisations is desirable

## A Success Story

ADR Reporting and Monitoring at JSS Medical College Hospital

### ADR Reporting and Monitoring

- Established in 1200 bed teaching / referral hospital
- Managed by Department of Clinical Pharmacy
- Introduced in November 1997
- Probably the first of its kind in the country
- Part of Comprehensive patient care management programme

## ADR Monitoring in JSS Hospital

- Spontaneous reporting system followed
- Reporting by all healthcare professionals
- Encouraged to report all kinds of reactions
- Have been advocating safe and quality use of medicines since 1997

### Methodology

- Circulars
- Personal visits
- ADR notification form was designed

## Methodology

- Operational modalities published in Clinical Pharmacy newsletter
- Reports are received verbally, by phone, completed forms, SMS
- Published literature and 'thank you' note to the reporting doctor
- Documentation on specially designed form and electronic format
- Follow-up of patients
- Quality assurance audit
- Reported ADR published in Clinical Pharmacy newsletter

## Problems identified

- Not aware of the ADR monitoring system
  Campaigning
- Lack of time
  Simple Procedure
- Non availability of ADR notification forms
  ADR forms attached to in-patient case notes

## You do not need to be certain!

- Have a high index of suspicion
- Report any suspected ADR
- Be a life saver

## Can I make a difference?

**YES**

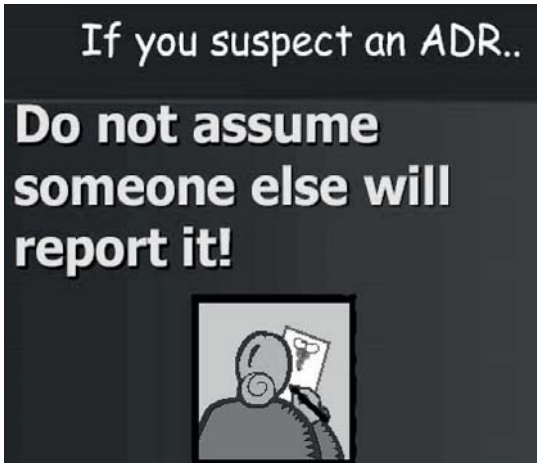
**YOU CAN**


HAVE A HIGH INDEX OF SUSPICION FOR ADVERSE DRUG REACTIONS

*BEING SUSPICIOUS PROMOTES SAFE USE OF DRUGS*

I THOUGHT DRUGS ARE SAFE .....
BUT I AM WRONG

Look for potential ADRs and report them





**DID YOU SUSPECT AN ADVERSE DRUG REACTION TODAY**

## Problems identified

- ADR considered to be trivial
  - Importance of reporting of ADRs
- Rare occurrence of ADR
  - High index of suspicion for ADR
- Fear of litigation
  - WHO Definitation of ADR

## Results

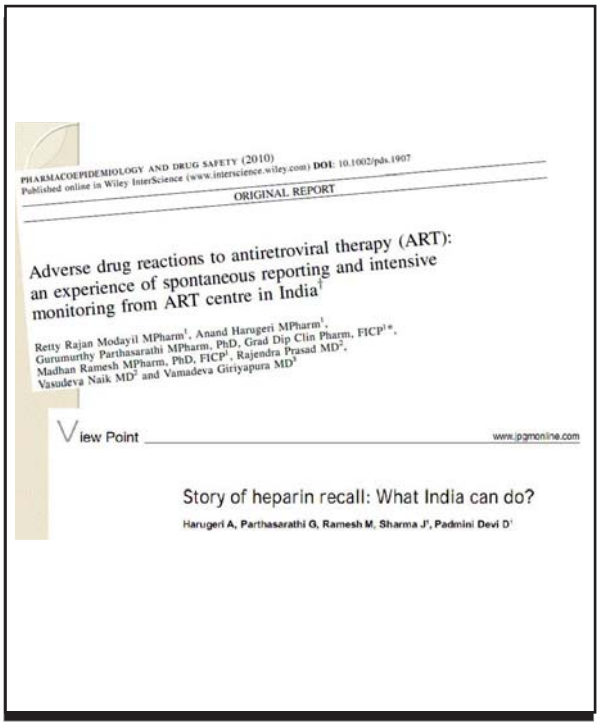
- 23572 reactions were evaluated until December 2016
- 62% were written reports and 38% were reported verbally

## Areas of Research

- ADR Related Hospital Admissions
- ADR - Cost implications
- ADR Related Emergency Admissions
- ADR - Predictability and Preventability
- Medication Related GI Bleeding
- Elderly and the ADEs & cost implications
- Pediatrics and ADEs & cost implications

## Areas of Research

- Intensive monitoring in Neuropsychiatry
- Adverse events following immunization in pediatric population
- Spontaneous reporting of ADRs in HIV positive patients on ART
- Intensive monitoring of ADRs in HIV positive patients on ART
- Medication safety in HIV patients with Tuberculosis
- Integrating Pharmacovigilance in Public Healthcare


PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2010)
Published online in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1907

ORIGINAL REPORT

Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India†

Retty Rajan Modayil MPharm[1], Anand Harugeri MPharm[1], Gurumurthy Parthasarathi MPharm, PhD, Grad Dip Clin Pharm, FICP[1]*, Madhan Ramesh MPharm, PhD, FICP[1], Rajendra Prasad MD[2], Vasudeva Naik MD[2] and Vamadeva Giriyapura MD[3]

View Point www.ijpmonline.com

Story of heparin recall: What India can do?

Harugeri A, Parthasarathi G, Ramesh M, Sharma J[1], Padmini Devi D[1]


Case Report

Sparfloxacin induced toxic epidermal necrolysis

M. Ramesh, G. Parthasarathi, B. Mohan,* A. B. Harugeri

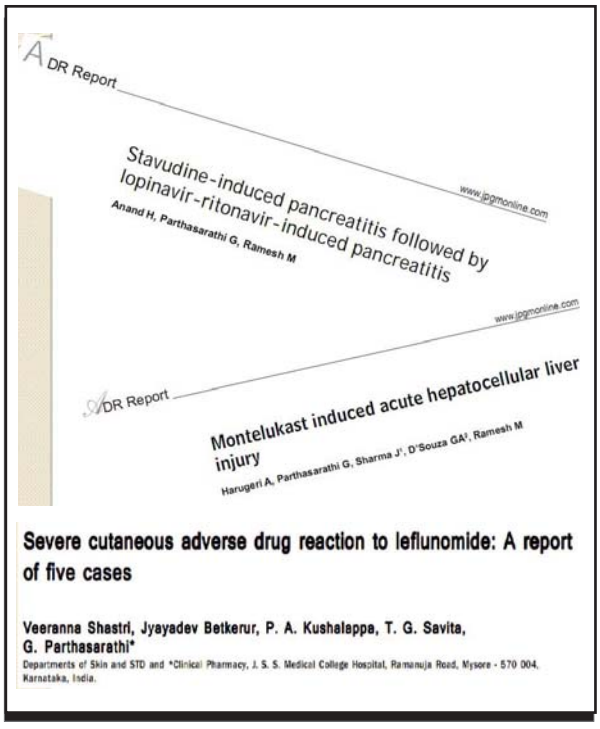
Department of Clinical Pharmacy, J. S. S. Medical College Hospital, Mysore, India and Department of *Medicine, Holdsworth Memorial Hospital, Mysore, India.

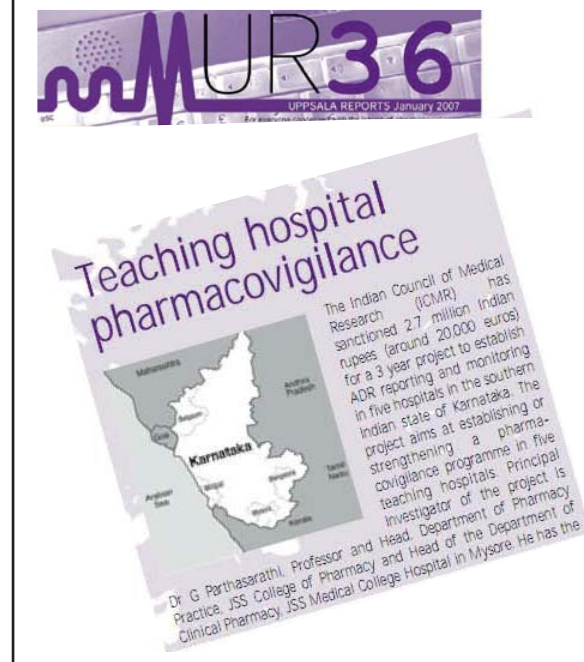
CASE REPORT

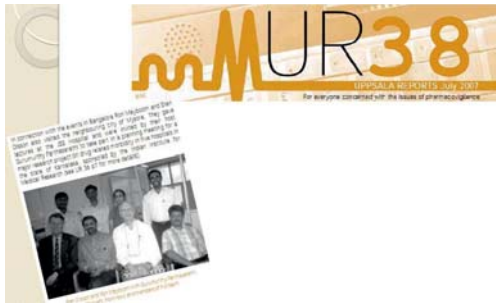
Valproic acid-induced abnormal behavior

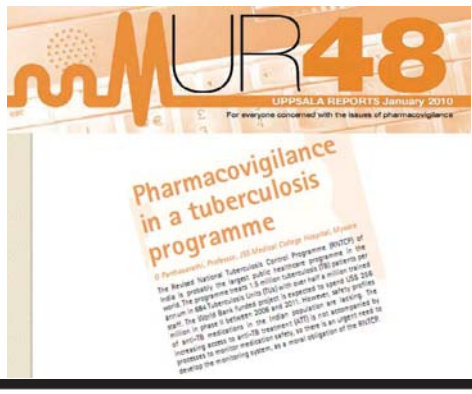
Nanjangud Chandrashekar Nagalakshmi, Madhan Ramesh, Gurumurthy Parthasarathi, Anand Harugeri, Mary Sam Christy, Belur Seshachala Keshava[1]

Department of Pharmacy Practice, J.S.S. College of Pharmacy, and [1]Department of Neurology, JSS Medical College Hospital, JSS University, Mysore, India




## Conclusion

- Hospital based pharmacovigilance programme is very vital
- Commitment is the 'key'
- Patient safety is a 'journey' not a 'destination'

# TERMINOLOGIES USED IN PHARMACOVIGILANCE

by

**Mr. Krishna Undela,**
**Lecturer, Pharmacy Practice, JSS College of Pharmacy, JSS University, Mysuru**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Adverse Drug Reaction

A response to a drug which is noxious and unintended and which **occurs at doses normally used** in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function

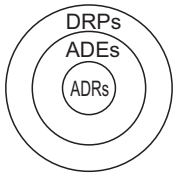
Ex : Thalidomide - Birth defects

**WHO Technical report 498 [1972]**

## Adverse Drug Event

Any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment

Ex: Sedatives - Accidents




**International Conference on Harmonisation 1994**

## Side Effect

Any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is **related to the pharmacological properties of the drug**

Ex : Hypoglycemia with Insulin

**http://www.who-umc.org/**

## Pharmacovigilance

The science and activities relating to the

detection,
assessment,
understanding and
prevention

of adverse effects or any other drug related problem

**World Health Organization 2002**

## Types of ADRs

- **Type A (Augmented)**
  - A dose-related reaction
  - **Features** - common, related to a pharmacological action of the drug, predictable and with low mortality
- **Type B (Bizaree)**
  - A non-dose-related reaction
  - **Features** - uncommon, not related to a pharmacological action of the drug, unpredictable and with high mortality
- **Type C (Chronic)**
  - A dose- and time-related reaction
  - **Features** - uncommon and related to the cumulative dose

## Types of ADRs

- **Type D (Delayed)**
  - A time-related reaction
  - **Features** - uncommon, usually dose-related and they occur or become apparent sometime after the use of the drug
- **Type E (End of Life)**
  - A withdrawal reaction
  - **Features** - uncommon and occur soon after withdrawal of the drug
- **Type F (Failure)**
  - A unexpected failure of therapy reaction
  - **Features** - common, dose-related and often caused by drug interactions

## Assessment of ADRs

**Predisposing Factors**

Any aspect of the patient's history (other than the drug) which might explain reported adverse events

Ex: Genetic factors, diet, alcohol consumption, disease history, polypharmacy or use of herbal medicines

**Dechallenge**

The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed

**Rechallenge**

The point at which a drug is again given to a patient after its previous withdrawal

## Assessment of ADRs

- Causality Assessment
  1. WHO Probability Scale
  2. Naranjo's Scale
  3. Karch & Lasagna's Scale
- Severity Assessment
- Predictability
- Preventability

## ADR Terminologies

**Suspected Adverse Reaction (SAR)**

A noxious and unintended response to any dose of a drug or biologic product for which there is a reasonable possibility that the product caused the response

**unexpected Adverse Reaction (UAR)**

A adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization or expected from characteristics of the drug

## ADR Terminologies

**Serious Adverse Reaction Event or Reaction (SAE/SAR)**

A serious adverse event or reaction is any uptoward medical Occurrence that at any dose:

- result in death
- requires inpatient hospitalisation
- prolongation of existing hospitalsation
- results in persistent or significant disability/incapacity
- is life-threating

**Suspected unexpected Serious Adverse Reaction (SUSAR)**

A reaction which is both unexpected and serious in nature

## ADR Reports

**Individual Case Safety Report (ICSR)**

Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.

**Periodic Safety Update Report (ICSR)**

Format and content for providing an evaluation of the risk benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase

## Risk

**Risk**

Probability of developing an outcome; unlike harm, does not involve severity of an outcome

**Absolute Risk**

Risk in a population of exposed persons [A/(A+B)]

**Reference (baseline) Risk**

- Risk in a population of unexposed persons [C(C+D)]
- Unexposed population refers to a reference population (as closely comparable with the exposed population as possible, apart from the exposure)

## Risk

**Attributable (excess) risk**

- Difference between the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk)
- Calculated as [A/(A+B)] - [C/(C+D)]

**Relative risk or risk ratio**

- Ratio of the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk)
- Calculated as [A/(A+B)] - [C/(C+D)]

## Organizations

**WHO**

- Established its programme for International Drug Monitoring in response to the thalidomide disaster detected in 1961
- Together with the WHO Collaborating centre for International Drug Monitoring (UMC), Uppsala, WHO promotes PV at the country level
- Currently, 127 countries are full members of the WHO Programme for International Drug Monitoring

https://www.who-umc.org/
http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

## Organizations

**CIOMS**

- Council for International Organizations of Medical Sciences
- Body set up under World Health Organizations
- CIOMS has run a program focusing on drug safety since the early 1980s
- Published may Guidelines for practice

https://cioms.ch/pharmacovigilance/

## Organizations

**ICH**

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Inception in 1990
- E2A - E2F Guidelines for Pharmacovigilance

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

## Organizations

**European Medicines Agency (EMA)**

- EMA provides extensive guidance to enable all stakeholders to meet their legal Pharmacovigilance obligations

**Good Pharmacovigilance Practices**

- Set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU)

**EudraVigilance**

- It is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the European Economic Area (EEA)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de

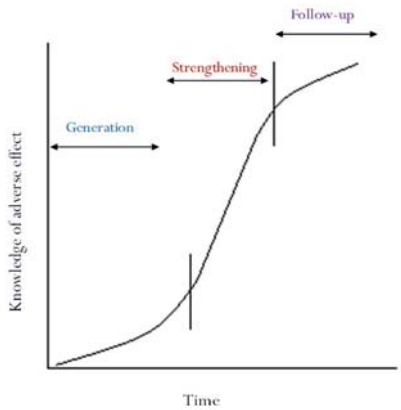
## Signal

**Definition**

Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify

## Signal

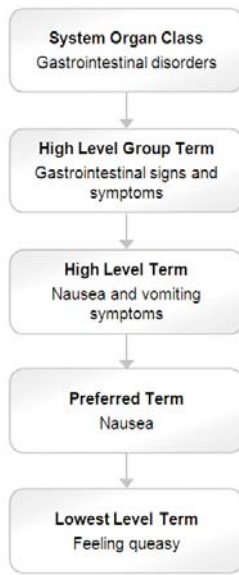
- Detection
- Validation
- Confirmation
- Analysis and prioritization
- Assessment
- Recommendation for action




## Tools

**MedDRA**

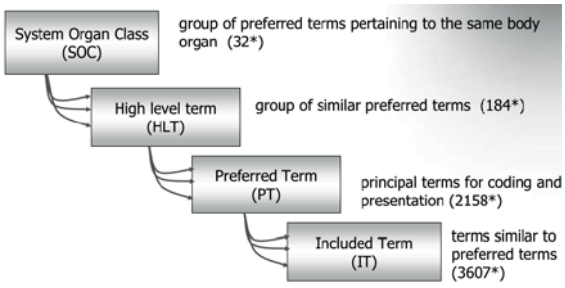
- Medical Dictionary for Regulatory Activities
- Adverse Event classification dictionary developed by ICH in 1990's
- A rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans



## Tools

**WHO-ART**

- It is a dictionary meant to serve as a basis for rational coding of adverse reaction terms
- The system is maintained by the UMC



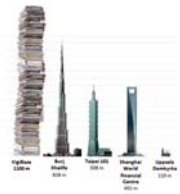

## Tools

**VigiFlow**

It is a management system for recording, processing and sharing reports of adverse effects

**VigiBase**

- Individual Case Safety Report (ICSR) database that contains ICSRs submitted by the participating member states enrolled under WHO's international drug monitoring programme
- It is the single largest drug safety data repository in the world



## Tools

**VigiLyze**

- Facilitate search, analysis and the extraction of useful information from the big VigiBase dataset

**VigiAccess**

(http://www.vigiaccess.org/)

- This database allows you to browse and view data on suspected side-effects from various medicinal products
- All data contained herein is sourced from VigiBase

## QPPV

- In the European Union, the Qualified Person Responsible For Pharmacovigilance (QPPV) is an individual, usually an employee of a pharmaceutical company, who is personally responsible for the safety of the human pharmaceutical products marketed by that company in the EU
- The holder of a marketing authorization for a drug for human use must have a QPPV
- The QPPV must reside in the European Union

# PHARMACOVIGILANCE METHODS

by

**Mr. Krishna Undela,**
**Lecturer, Pharmacy Practice, JSS College of Pharmacy, JSS University, Mysuru**
(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Introduction

How can you monitor the safety of drugs after registration?

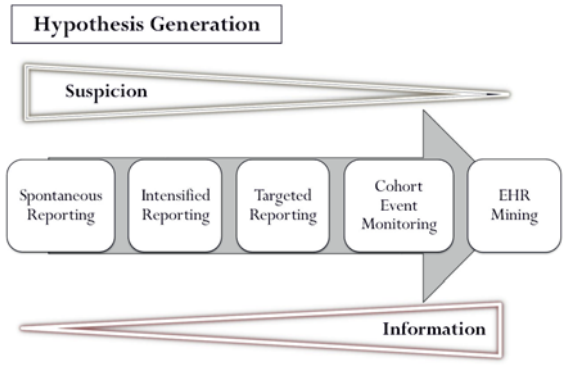
Post-marketing surveillance studies

Hypothesis generation

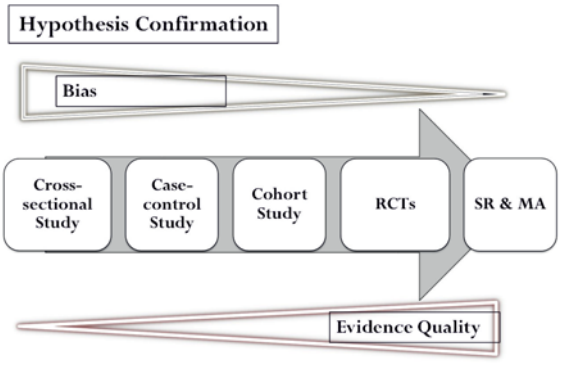
Hypothesis confirmation

Ex: SGLT2 Inhibitors can cause acute kidney injury?

## PV Methods Spectrum




## PE Methods Spectrum




## What is your Objective?

- To establish a functional reporting system to monitor the safety of all medicines? _____
- To learn more about the safety profile of new medicines in the early post-marketing phase? _____
- To learn more about the ADR profile of specific medicines in your population? _____

## What is your Objective?

- To estimate the incidence of a known ADR to a specific medicine in your population? _____
- To gather more information on the safety profile of a new chemical entity in an early post-marketing phase? _____
- To utilize electronic health records and registres to support pharmacovigilance activities? _____

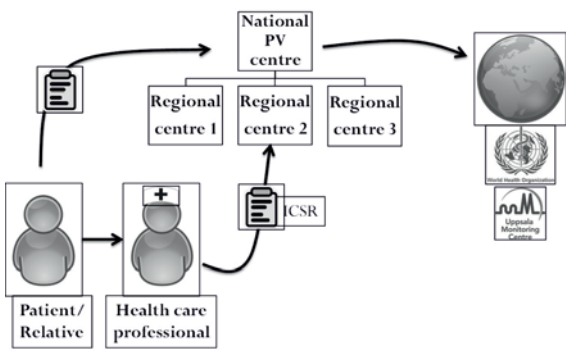
## Spontaneous Reporting

'an unsolicited communication by healthcare professionals or consumers that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme'

OR

'a clinical observation that originates outside of a formal study'

## Spontaneous Reporting




## Spontaneous Reporting: What to Report?

**Developing Pharmacovigilance System**

- All suspected ADRs
  - Encourage a culture of ADR reporting
  - Build PV capacity
  - Develop a profile of ADRs experienced with locally used medicines

When in doubt -> Report

When something concerns you -> Report

## Spontaneous Reporting: What to Report?

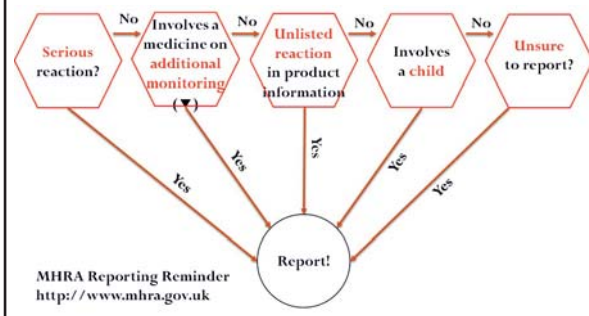
Established Pharmacovigilance Systems

- May wish to restrict what to report
  Ex: ADRs to new medicines
  ADRs occurring in children
  Serious suspected ADRs

When in doubt -> Report

When something concerns you -> Report

## Spontaneous Reporting: What to Report?




## Spontaneous Reporting

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2003; 12: 687–692
Published online 16 July 2003 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/pds.871

ORIGINAL REPORT

### Adverse drug reactions in a South Indian hospital—their severity and cost involved†

M. Ramesh*, Jayesh Pandit and G. Parthasarathi

*Department of Pharmacy Practice, JSS College of Pharmacy, Mysore, India*

**Purpose** The study was aimed to assess the pattern of occurrence of adverse drug reactions (ADRs) in the local population, severity of reported ADRs and additional financial resource utilisation associated with ADRs.
**Methods** This was a prospective, spontaneous reporting study conducted over a period of 7 months by clinical pharma-

**Results** A total of 270 suspected ADRs were reported and evaluated from 164 patients. A total of 3.7% of the hospitalised patients experienced an ADR, 0.7% of the admissions were due to ADRs and 1.8% had a fatal ADR. The gastrointestinal

## Spontaneous Reporting

| | |
|---|---|
| Pros | • Covers the whole population<br>• Includes all medicines<br>• Continual monitoring throughout life-cycle of a medicine<br>• Detect signals of new, rare, or serious ADRs<br>• Most commonly used method<br>• Easiest method to establish<br>• Relatively inexpensive<br>• Least labour intensive |
| Cons | • Inherent under reporting<br>• Captures only suspected ADRs<br>• Reporting bias<br>• Denominator unknown<br>• Difficult to detect<br>- delayed ADRs<br>- ADRs with high background incidence |

## Intensified Reporting

- Extension of Spontaneous Reporting Programme
- Black Triangle Scheme

▼ This medicinal product is subject to additional monitoring

Ex:

- Medicines containing a new active substance
- Biological medicines
- Medicines given conditional approval or approved under exceptional circumstances
- Medicines that require additional studies (e.g. More data on long term use or on a rare side effect seen in clinical trials)

## Intensified Reporting


## Intensified Reporting

HIGHLIGHTS OF PRESCRIBING INFORMATION

**CAPOTEN® TABLETS** ▼℞
**(captopril tablets)**

**WARNING: USE IN PREGNANCY**
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

**RECENT LABELING CHANGES**
Indications (1.x)
Warnings/Precautions (5.x, 5.y, 5.z)
Adverse Reactions (6.x)

**INDICATIONS AND USAGE**
- Hypertension (caution in renally-impaired patients), alone or in combination with other anti-hypertensives (1.1)
- Congestive Heart Failure, usually in combination with diuretics and digitalis (1.2)
- Left Ventricular (LV) Dysfunction after Myocardial Infarction to improve survival and reduce morbidity in clinically stable patients with LV ejection fraction ≤ 40% (1.3)
- Diabetic Nephropathy (Type I IDD with proteinuria > 500 mg/day and retinopathy) (1.4)

**DOSAGE AND ADMINISTRATION**
General: Take 1 hour before meals. Individualize dosage.

| Indication | Initiation of Therapy | Usual Daily Dose | Do Not Exceed |
|---|---|---|---|
| Hypertension | 25 mg bid or tid | 25-150 mg bid or tid* | 450 mg/ day |
| Heart Failure | 25 mg tid | 50-100 mg tid | 450 mg/ day |
| LV Dysfunction after MI | 12.5 mg tidt | 50 mg tid | |
| Diabetic Nephropathy | | 25 mg tid | |

* Usual daily dosing does not exceed 50 mg BID or TID. Consider adding a thiazide-type diuretic. (2.2)
† A single dose of 6.25 mg should precede initiation of 12.5 mg therapy. (2.4)
**Adjust dose in renal impairment (2.6, 5.7)**

**HOW SUPPLIED**
Tablets: 12.5, 25, 50, 100 mg; scored (3)

**CONTRAINDICATIONS**
Known hypersensitivity (e.g., angioedema) to any ACE inhibitor.

**WARNINGS/PRECAUTIONS**
- Angioedema with possibility of airway obstruction (5.1)
- Neutropenia (<1000/mm³) with myeloid hypoplasia (5.2)
- Excessive hypotension (5.4)
- Fetal/Neonatal Morbidity and Mortality (5.5)
- Hepatic failure (5.6)
- Use with caution in renal impairment. (2.6, 5.7)
- Hyperkalemia (5.8)
- Cough (5.9)

***Most Common Adverse Reactions (≥ n/100) (6)***
- rash (sometimes with arthralgia and eosinophilia), taste impairment (distortion or loss), cough, pruritus, chest pain, palpitations, tachycardia, proteinuria

***To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at 1-800-FDA-1088***

**DRUG INTERACTIONS**
- Diuretics (6.1)
- Other vasodilators (6.2)
- Agents Causing Renin Release (6.3)
- Beta-Blockers (6.4)
- Agents Increasing Serum Potassium (6.5)
- Lithium (6.7)

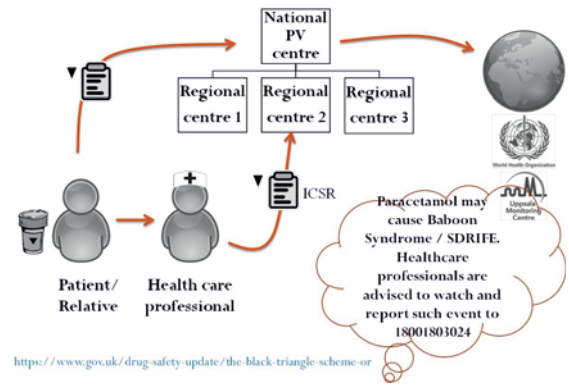
**USE IN SPECIFIC POPULATIONS**
- Pregnancy: Fetal/Neonatal Morbidity and Mortality (5.5)
- Lactating Women: Potential for serious adverse reactions in nursing infants. (7.3)
- Pediatric Use: Safety and effectiveness not established. Use only if other measures ineffective. (7.4)
- Renal-impairment: Use with caution. (2.6, 5.7)

**See P for PATIENT COUNSELING INFORMATION**

***These highlights do not include all the information needed to prescribe Capoten safely and effectively. See Capoten's comprehensive prescribing information provided below.***

m/yy

## Intensified Reporting



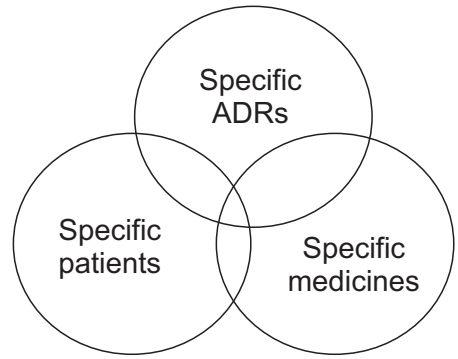

https://www.gov.uk/drug-safety-update/the-black-triangle-scheme-or

## Intensified Reporting

| | |
|---|---|
| Pros | • Covers the whole population<br>• ~~Includes all medicines~~<br>• ~~Continual monitoring throughout life-cycle of a medicine~~<br>• Detect signals of new, rare, or serious ADRs<br>• Most commonly used method<br>• Easiest method to establish<br>• Relatively inexpensive<br>• Least labour intensive |
| Cons | • ~~Inherent under reporting~~<br>• ~~Captures only suspected ADRs~~<br>• Reporting bias<br>• Denominator unknown<br>• Difficult to detect<br>- delayed ADRs<br>- ADRs with high background incidence |

## Targeted Reporting

- Builds on principles of spontaneous reporting
- Intensified ADR Reporting within a defined cohort



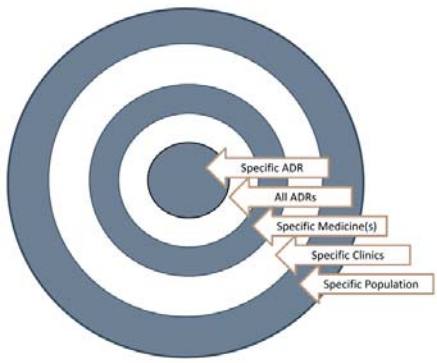

## Targeted Reporting

Drug Saf (2015) 38:395–408
DOI 10.1007/s40264-015-0277-9

ORIGINAL RESEARCH ARTICLE

**Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda**

**Helen Ndagije · Victoria Nambasa · Elizabeth Namagala · Huldah Nassali · Dan Kajungu · Gordon Sematiko · Sten Olsson · Shanthi Pal**




## Targeted Reporting

*Methods* From April 2012 to March 2014, all cases of suspected renal toxicity in 10,225 patients on tenofovir-based regimens were monitored in the regional pharmacovigilance

*Results* There was one suspected renal toxicity reported for every 200 patients on a tenofovir-based regimen. Some of the serious reactions reported were death in two cases and bone demineralisation in five patients. Most of patients

## Targeted Reporting

| Pros | Cons |
|---|---|
| Can utilise existing ADR reporting infrastructure | Under-reporting remains a problem |
| Targets specific medicines of interest | Captures only suspected ADRs or known toxicities |
| Possible to implement monitoring programme that targets specific issue of concern (ADR, medicine, patient group) | May limit reporting only to specific ADRs |
| Captures useful information (less background noise) | Relies on diagnostic capability of reporter |
| Denominator known | |

## Cohort Event Monitoring (CEM) Also called as 'Prescription Event Monitoring (PEM)'

*A prospective, longitudinal, observational, cohort study of adverse events associated with one or more monitored medicines*

| | |
|---|---|
| Prospective | 'Real-time monitoring' |
| Longitudinal | Over a period of time |
| (Inceptional) | From starting of treatment |
| Observational | Dose not interfere with patient management |
| Cohort | Defined group of patients |
| Adverse events | Any new clinical experience (favourable or unfavourable) that is worthy of a record in the patient's life, regardless of its severity and without judgment on its causality |
| Monitored medicine | Specific medicine(s) |

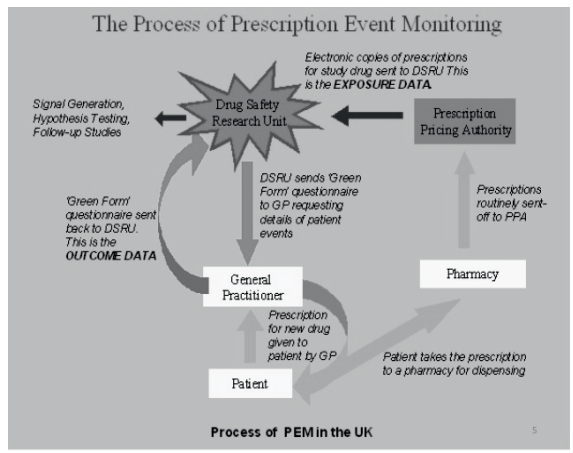
## Cohort Event Monitoring

- New class of medicine
- Medicine related to class of medicine that has previously caused problems
- Potentially significant adverse event observed during pre- or post-marketing surveillance (SR)

*A time-limited programme to complement other PV activities; not intended to replace spontaneous reporting*

- *NZ Intensive Medicines Monitoring Programme (IMMP), Dunedin, 1977*
- *Drug Safety Research Unit, Southampton, UK, 1980*
- *J-PEM, Tokyo, Japan, 1999*

## Cohort Event Monitoring



## Cohort Event Monitoring

**Objectives:**

- Characterise known reactions
- Detect signals of unrecognised reactions
- Identify interactions with other medicines
- Detect inefficacy of medicine
- Assess safety in pregnancy & lactation
- Measure risk (including comparative risk)
- Identify risk factors for ADRs

## Cohort Event Monitoring

**Safety Profile of Artemether-Lumefantrine: A Cohort Event Monitoring Study in Public Health Facilities in Tanzania**

Alambo K. Mssusa[1] · Adam M. Fimbo[2] · Alex F. Nkayamba[1] · Henry F. Irunde[3] · Hiiti B. Sillo[2] · Danstan H. Shewiyo[4] · Geraldine Hill[5] · Omary M. Minzi[6]

*Methodology* Patients who presented to public health facilities in four regions of Tanzania who were prescribed AL were enrolled in a CEM study, a prospective, obser-

*Results* A total of 8040 patients were enrolled in the study, of whom 6147 were included in the analysis. Following treatment initiation, a total of 530 AEs were reported in 6 % (383) of the patients. The most frequent post-treatment AEs

Clin Drug Investig (2016) 36:401–411

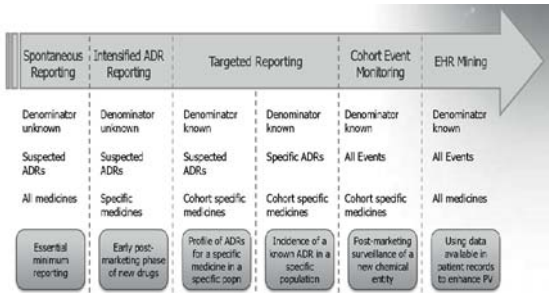
## Cohort Event Monitoring

| Pros | Cons |
|---|---|
| Early detection of signals of unsuspected ADRs | More labour intensive than SR or TSR |
| Denominator information allows incidence rates of ADRs to be calculated | More costly |
| Near complete profile of AEs/ADRs for medicine of interest | Much data collected most of which represents 'background noise' |
| Assessment of risk; identification of risk factors; between drug comparisons | New to health professionals and PV centres |
| Pregnancy outcomes | Training required |
| Deaths recorded | LTFU may be substantial and needs to be actively managed |

## Electronic Health Record Mining

- Electronic Health Records – a potentially rich source of ADR data
- Data generally collected for reasons other than pharmacovigilance
- Much data, mostly not ADRs – Needle in a haystack!
- How to find the needles is an area of active research

## PV Methods Spectrum




## PV Methods Spectrum

| Method | Medicines | Population | Reports |
|---|---|---|---|
| Spontaneous Reporting | All medicines (life cycle of product) | All exposed individuals (denominator is unknown) | All ADRs |
| Intensified Reporting | Specific medicines | All exposed individuals (denominator is unknown) | All ADRs |
| Targeted Reporting | Specific medicines | Specific population (denominator is known) | All ADRs Specific ADRs |
| Cohort Event Monitoring | Specific medicines | Specific population (denominator is known) | All events |
| HER Mining | All medicines | Specific population (denominator is known) | All events |

## What is your Objective?

- To establish a functional reporting system to monitor the safety of all medicines?
  **Spontaneous Reporting**
- To learn more about the safety profile of new medicines in the early post-marketing phase?
  **Intensified Reporting**
- To learn more about the ADR profile of specific medicines in your population?
  **Targeted Reporting**

## What is your Objective?

- To estimate the incidence of a known ADR to a specific medicine in your population?
  **Targeted Reporting**
- To gather more information on the safety profile of a new chemical entity in an early post-marketing phase?
  **CEM**
- To utilize electronic health records and registres to support pharmacovigilance activities?
  **EHR Mining**

# ADVERSE EVENTS: WHAT, WHERE & WHEN TO REPORT

by

**Dr. K. M. Sudha,**
**Professor of Pharmacology, Coordinator – Pharmacovigilance Programme of India (PvPI)**
**Institute of Pharmacology, Madras Medical College, Chennai**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Definitions of Adverse Events

- Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related

  21 CFR 312.32(a)

- Indicates a change in the subject's health status 'since baseline' right before taking the study drug.

- When toxicity of the study drug is a hypothesis you will see on the calendar, a baseline physical exam to be completed either at Day 0 or Day 5 prior to dosing

## Definitions of Adverse Events

Baseline would include all of the below:

- Pre-existing conditions that are ongoing during the clinical trial
  - Hypertension
  - Diabetes

- Concomitant medications taken prior to participation in the clinical trial
  - Anticoagulants to prevent thrombosis
  - Steroids for autoimmune condition

## Definitions of Adverse Events

Examples of Adverse Events which are not related to [or caused by] the study drug but if they occur while the subject is on study, would have to be collected, reviewed by PI and tracked:

- Transfusion reactions
- Accidental injuries
- Surgery

## Adverse Event (AE)

Any untoward medical occurrence including

- a symptom or
- disease or
- an abnormal laboratory finding

during treatment with a medicinal product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given.

- CDSCO & FDA

AE - Related or unrelated to the drug being given

## Adverse Event (AE)

An adverse event can arise with

- any use of the drug (e.g., off-label use, use in combination with another drug)
- any route of administration
- any formulation
- any dose including an overdose

.

Also known as adverse experience

**- FDA**

## Why do we collect Adverse Event data?

- To determine the safety profile of a drug or device
- To evaluate the risks and benefits of a product
- To provide information for the package insert, if approved for marketing

Determination of safety is often one of the primary protocol objectives when evaluating new therapies

**Protecting <u>subject safety</u> is one of the most important responsibilities of an investigator**

**Institutional Review Boards (IRBs) also share the responsibility**

- Ensure studies do not expose subjects to **undue harm**
- Ensure the **risk-benefit ratio** falls within an acceptable range

## Synonyms of Adverse "Event" include:

- Effect
- Experience
- Health consequence
- Occurrence
- Outcome
- Reaction (to a drug)

**21 CFR 312 vs. 21 CFR 314**

These two regulations define different adverse event terms, as shown in Table 1:

**Table 1. 21 CFR 312 and 21 CFR 314 Adverse Event Terms**

| Term | 21 CFR 312 | 21 CFR 314 |
|---|---|---|
| Adverse event | √ | |
| Adverse drug experience | | √ |
| Life-threatening adverse event | √ | |
| Life-threatening adverse drug experience | | √ |
| Life-threatening suspected adverse reaction | √ | |
| Serious adverse event | √ | |
| Serious adverse drug experience | | √ |
| Serious suspected adverse reaction | √ | |
| Suspected adverse reaction | √ | |
| Unexpected adverse event | √ | |
| Unexpected adverse drug experience | | √ |
| Unexpected suspected adverse reaction | √ | |

Both 21 CFR 312 and 21 CFR 314 apply to many industry-sponsored and other studies.

Although the wording of 21 CFR 312 and 21 CFR 314 terms vary, the core concepts of similar terms are the same, e.g.:

Goldfarb, 2012, pg. 3,15

### Examples of AEs:

- Abnormal lab value
- Worsening of pre-existing condition
- Physical sign or symptom
- Concurrent illness
- Subjective report
- Change in vital signs or physical exam

### Examples of AEs:

- Complication from surgery or procedure
- Psychological symptoms or harm
- Device malfunction/failure
- Device user error
- Incorrect dose or overdose
- Drug dependence

*Important to know the subject's baseline conditions and concomitant medications (time of enrollment)!

### Where are you going to identify AEs?

- Medical Records
  - Lab reports, radiology reports, progress notes, surgical reports
- Subject questionnaires
- Subject diaries
- Medication reconciliation
- Observation
- Specific information for Case Report Forms (CRFs)
- Open ended questions to subject and family
  - "How have you been feeling since I saw you last?"
  - "Can you describe any changes since you started the study medication?"

### How are you going to identify AEs?

- Develop a systematic method for collecting information
  - Use tools to ensure thoroughness
- Practice open ended questions
- Avoid leading questions:
  - "Are you experiencing nausea?"
- Remain objective
- Take time to reassure the patient and listen

## Documenting AEs:

Adverse Event Form

STUDY NAME

Site Name:_____

Pt_ID:_____

This form is cumulative and captures adverse events of a single participant throughout the study.

| Severity | Study Intervention Relationship | Action Taken Regarding Study Intervention | Outcome of AE | Expected | Serious Adverse Event (SAE) |
|---|---|---|---|---|---|
| 1 = Mild<br>2 = Moderate<br>3 = Severe<br>4 = Life-Threatening | 0 = Not related<br>1 = Unlikely related<br>2 = Possibly related<br>3 = Probably related<br>4 = Definitely related | 0 = None<br>1 = Dose modification<br>2 = Medical Intervention<br>3 = Hospitalization<br>4 = Intervention discontinued<br>5 = Other | 1 = Resolved<br>2 = Recovered with minor sequelae<br>3 = Recovered with major sequelae<br>4 = Ongoing/Continuing treatment<br>5 = Condition worsening<br>6 = Death<br>7 = Unknown | 1 = Yes<br>2 = No | 1 = Yes<br>2 = No<br>(If yes, complete SAE form) |

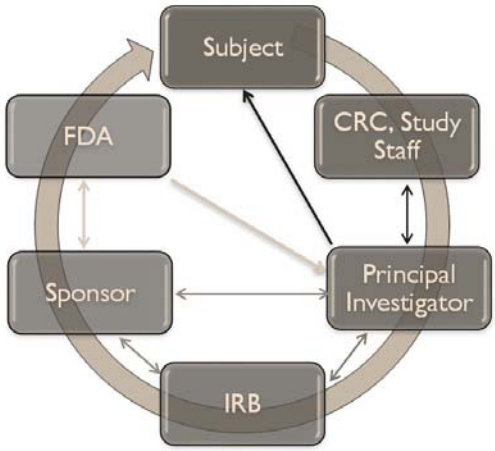
At end of study only: Check this box if participant had no adverse events ☐ None

| Adverse Event | Start Date | Stop Date | Severity | Relationship | Action Taken | Outcome of AE | Expected? | SAE? |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

## Documenting AEs:

- Event (nomenclature/description)
- Grading (Severity/Intensity)
- Relationship (Causality)
- Expected?
- Serious?
- Action taken (Treatment?)
- Duration
- Outcome

## Reporting AEs: All about safety!




## Reporting Responsibility:

Investigators and IRBs must promptly report information regarding AEs or unanticipated problems that involve risks to subjects or others

*All AEs should be reviewed by and signed by a qualified clinician/investigator

**Know the reporting requirements and timelines for your institution and study!

### Adverse Drug Reaction (ADR)

Any noxious, unintended or undesirable effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions

**- WHO**

## Suspected Adverse Reaction (SAR)

Suspected Adverse Reaction means any adverse effect for which there is a reasonable possibility that the drug caused the adverse event.

A suspected adverse reaction implies a **lesser degree of certainty** about causality than adverse reaction

- FDA

'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.

## Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (sADR)

An AE/ADR that is associated with

- Death
- life threatening
- hospitalisation /prolongation of hospitalisation
- persistent or significant disability or incapacity
- congenital anomaly or birth defect

- FDA & CDSCO

## A "Life Threatening Adverse Drug Experience" Defined

- Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, or it is suspected that the use or continued use of the product would result in the patient's death.

Example include:

- hemorrhaging and internal bleeding with rapid drop in blood pressure
- Loss of consciousness from increase in pressure on the brain

## Hospitalization Defined

Admission to the hospital for longer than 24 hours or prolongation of a hospital stay due to adverse event

## "Disability" Defined

- A substantial disruption of a person's ability to conduct normal life functions
- Examples include: loss of speech; fatigue so great the subject cannot get out of bed at all loss of memory; and paralysis

## "Congenital Anomaly" Defined

Exposure to a medical product prior to conception or during pregnancy resulting in an adverse outcome in the child

Thalidomide is the best example of a drug causing congenital anomalies with babies born with deformed arms and legs.

## Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)

Unexpected: An AE/SAR which is

- not listed in the investigators's brochure (IB) / patient information leaflet (PIL)
- not listed at the specificity or severity that has been observed

## Examples of an Unexpected Adverse Event

- **Hepatic necrosis** would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis
- Cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents

## Severe ≠ Serious!

* Severity refers to the intensity of an event
* Seriousness is a guide for defining regulatory reporting obligations
    - based on patient/event outcome or action

**Example:**
New onset migraine; lasting two days, causing subject to stay in bed and miss work, unable to care for children

- Not life threatening, No hospitalization, No persistent disability, ***Not Serious***
- But, intensity ***is Severe***

## Examples of Important Medical Events

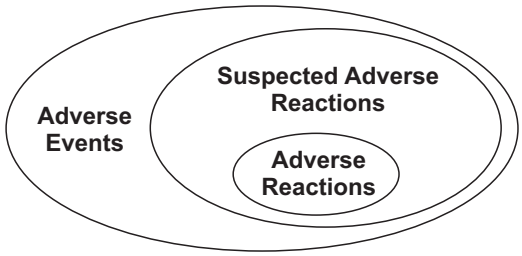
- Allergic bronchospasm requiring intensive treatment in an emergency room or at home

- Blood dyscrasias

- Convulsions that do not result in inpatient hospitalization

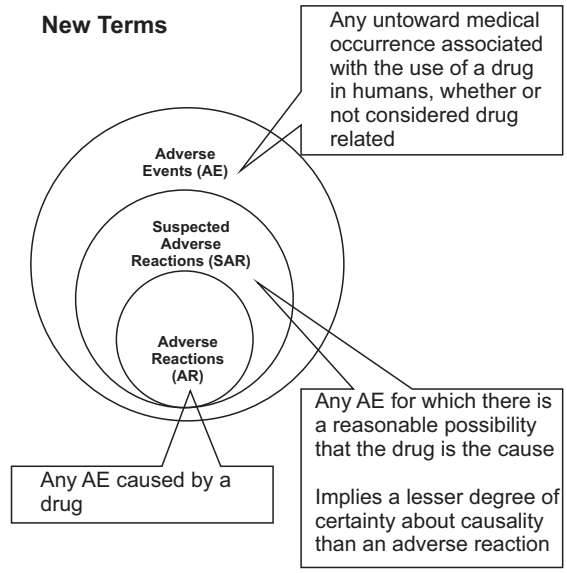
- Development of drug dependency or drug abuse

## The Universe of Adverse Events




## The Universe of Adverse Events

**New Terms**




National Cancer Institute March 28, 2011

## Difference between AE & ADR

**AE**

- Doesn't imply causal relationship
- Can occur with any dose / route of administration / formulation

**ADR**

- Causal relationship is suspected
- Can occur with normal dose / specified route & formulation

## Expected versus Unexpected:

- Expected AEs will be described in the following:
  - Investigator's Brochure (IB); contains information regarding all AEs reported in all trials of the test article, to date
  - Package Insert; safety and dosing information on all approved products
  - Protocol and Informed Consent

## Internal versus External AEs

In the context of a multi-center trial

- Internal AE is an event that is experienced by subjects enrolled at your institution
  - Also known as On-Site
- External AE in an event experienced by subjects enrolled at other institutions that are participating in the same multi-center trial
  - Also known as Off-Site

## Related terms

Unanticipated Problems (UAPs) involving risks to subjects or others:

Must meet all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency)
2. related or possibly related to participation in the research
3. suggests that the research places subjects at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

## Unanticipated Adverse Device Effect:

Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if not identified in the device brochure, protocol, or consent form

## AE & ADR – Why to report ?

- Ethical requirements
- Regulatory requirements
- Licensing Requirements

AE & ADR

- To reduce the drug related harm to the patient
- To encourage safe and rational use of medicines in the public

ADR

## AE – What to report

Minimum regulatory requirements of SAE to be reported:

- An identifiable patient
- An investigational drug
- A serious adverse event
- An identifiable reporter

## Data Elements for reporting SAE

**1. Patient Details**

- Initials & other relevant identifier * (hospital/OPD record number etc.)
- Gender
- Age and/or date of birth
- Weight
- Height

**- Schedule Y**

## Data Elements for reporting SAE

**2. Suspected Drug(s)**

- Generic name of the drug *
- Indication(s) for which suspect drug was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

**- Schedule Y**

## Data Elements for reporting SAE

**3. Other Treatment(s)**

Provide the same information for concomitant drugs (including non prescription/OTC drugs) and non-drug therapies, as for the suspected drug(s).

**- Schedule Y**

## Data Elements for reporting SAE

**4. Details of Suspected Adverse Drug Reaction(s)**

- Full description of reaction(s) including body site and severity, as well as the criteria for seriousness.
- In addition to a description, describe a specific diagnosis for the reaction. *
- Start date (and time) of onset of reaction.
- Stop date (and time) or duration of reaction.
- Dechallenge and rechallenge information.
- Setting (e.g., hospital, out-patient clinic, home, nursing home).

- Schedule Y

## Data Elements for reporting SAE

**5. Outcome**

- Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted.

- For a fatal outcome, cause of death and its possible relationship to the suspected reaction; any post-mortem findings.

- Schedule Y

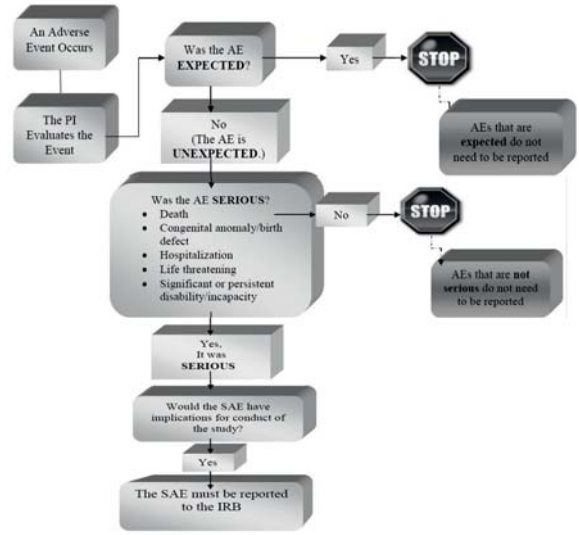
## Data Elements for reporting SAE

### 6. Details about the Investigator*

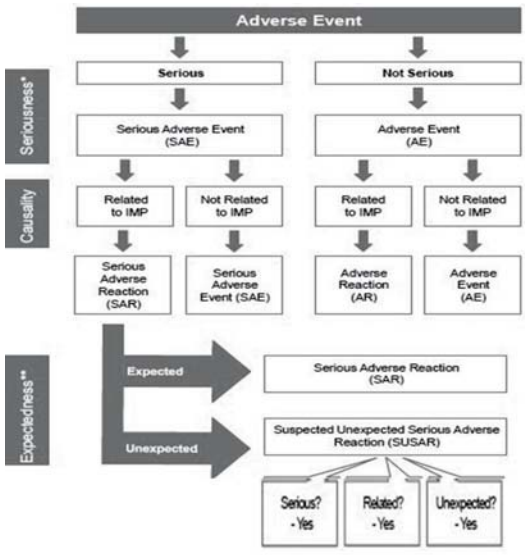
- Name
- Address
- Telephone number
- Profession (speciality)
- Date of reporting the event to Licensing Authority
- Date of reporting the event to Ethics Committee overseeing the site
- Signature of the Investigator

**- Schedule Y**

## AE – How to report ?

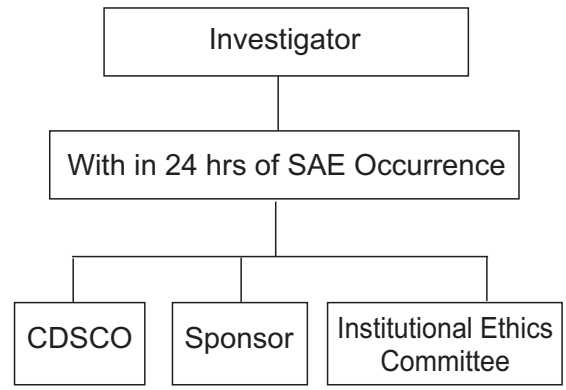



## AE – Assessment



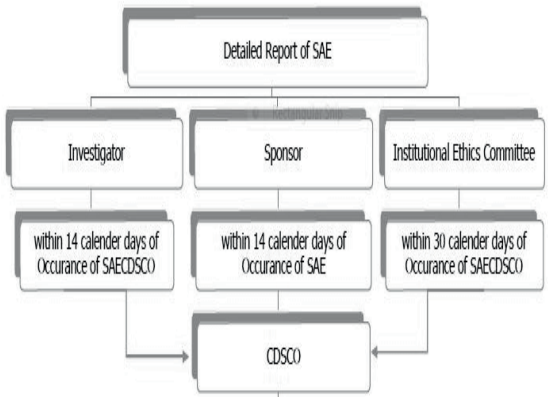

## AE – When to report ? (Timeline)

1. Initial report of AE:

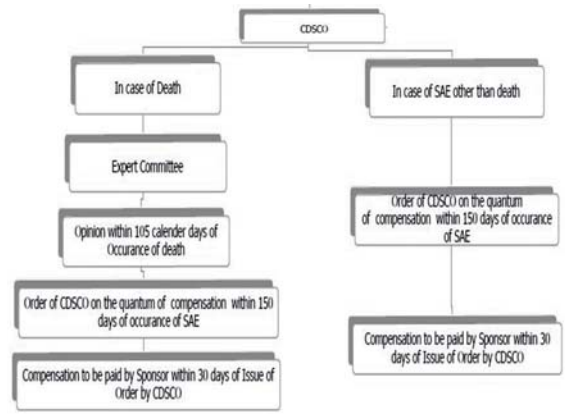


## AE-When to report:

### 2. Detailed Report of Serious Adverse Event (SAE)



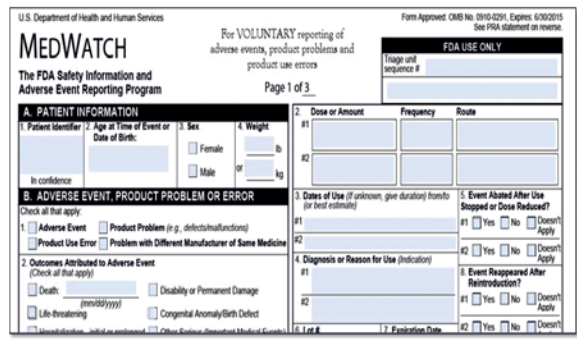

## 2. Detailed Report of Serious Adverse Event (SAE)…




## Formats of Submission an ISR

- Narrative
  - overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies
- FDA Form 3500a
- Council for International Organizations of Medical Sciences (CIOMS) I Form which is used with international studies
- Electronic format that FDA can process, review, and archive
  - Safety Reporting Portal (SRP) - pending for drugs/biologics

## Voluntary AE reporting: MedWatch Standard Form 3500


U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

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

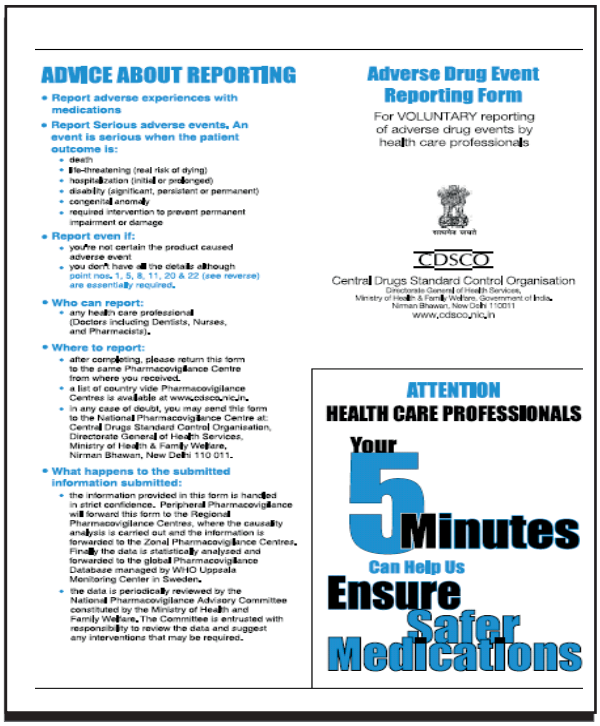
Form Approved: OMB No. 0910-0291, Expires: 6/30/2015 See PRA statement on reverse.

FDA USE ONLY

Page 1 of 3

A. PATIENT INFORMATION

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR



## ADVICE ABOUT REPORTING

- **Report adverse experiences with medications**
- **Report Serious adverse events. An event is serious when the patient outcome is:**
  - death
  - life-threatening (real risk of dying)
  - hospitalization (initial or prolonged)
  - disability (significant, persistent or permanent)
  - congenital anomaly
  - required intervention to prevent permanent impairment or damage
- **Report even if:**
  - you're not certain the product caused adverse event
  - you don't have all the details although point nos. 1, 5, 8, 11, 20 & 22 (see reverse) are essentially required.
- **Who can report:**
  - any health care professional (Doctors including Dentists, Nurses, and Pharmacists).
- **Where to report:**
  - after completing, please return this form to the same Pharmacovigilance Centre from where you received.
  - a list of country vide Pharmacovigilance Centres is available at www.cdsco.nic.in.
  - in any case of doubt, you may send this form to the National Pharmacovigilance Centre at: Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi 110 011.
- **What happens to the submitted information submitted:**
  - the information provided in this form is handled in strict confidence. Peripheral Pharmacovigilance will forward this form to the Regional Pharmacovigilance Centres, where the causality analysis is carried out and the information is forwarded to the Zonal Pharmacovigilance Centres. Finally the data is statistically analysed and forwarded to the global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.
  - the data is periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with responsibility to review the data and suggest any interventions that may be required.

## Adverse Drug Event Reporting Form

For VOLUNTARY reporting of adverse drug events by health care professionals

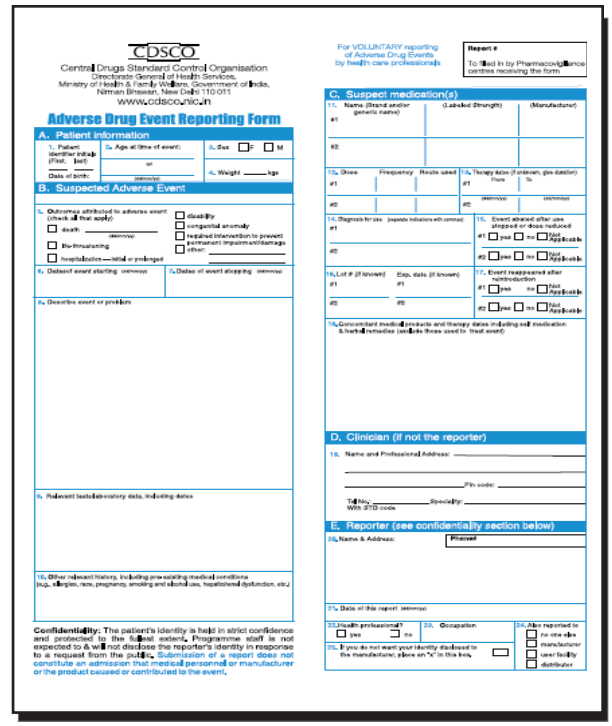
सत्यमेव जयते

CDSCO

Central Drugs Standard Control Organisation
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
Nirman Bhawan, New Delhi 110011
www.cdsco.nic.in

## ATTENTION
## HEALTH CARE PROFESSIONALS

Your **5 Minutes** Can Help Us **Ensure Safer Medications**



CDSCO

Central Drugs Standard Control Organisation
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
Nirman Bhawan, New Delhi 110 011
www.cdsco.nic.in

For VOLUNTARY reporting of Adverse Drug Events by health care professionals

Report #
To be filled in by Pharmacovigilance centres receiving the form

**Adverse Drug Event Reporting Form**

**A. Patient information**

1. Patient identifier Initials (First, last) / Date of birth: (dd/mm/yy)
2a. Age at time of event: / or
3. Sex ☐ F ☐ M
4. Weight ____ kg

**B. Suspected Adverse Event**

5. Outcomes attributed to adverse event (check all that apply)
☐ death (dd/mm/yy)
☐ life-threatening
☐ hospitalization — initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

6. Dateof event starting (dd/mm/yy)
7. Dateof of event stopping (dd/mm/yy)
8. Describe event or problem
9. Relevant tests/laboratory data, including dates
10. Other relevant history, including pre-existing medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

**Confidentiality:** The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to & 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 event.

**C. Suspect medication(s)**

11. Name (Brand and/or generic name) / (Labeled Strength) / (Manufacturer)
#1
#2
12. Dose / Frequency / Route used
13. Therapy dates (if unknown, give duration) From / To
14. Diagnosis for use (reason indication with comma)
15. Event abated after use stopped or dose reduced
16. Lot # (if known) / Exp. date (if known)
17. Event reappeared after reintroduction
18. Concomitant medical products and therapy dates (including self medication & herbal remedies (exclude those used to treat event))

**D. Clinician (if not the reporter)**

19. Name and Professional Address: / Pin code:
Tel No. With STD code / Speciality:

**E. Reporter (see confidentiality section below)**

20. Name & Address: / Phone#
21. Date of this report (dd/mm/yy)
22. Health professional? ☐ yes ☐ no
23. Occupation
24. Also reported to ☐ the site q/a ☐ manufacturer ☐ user facility ☐ distributor
25. If you do not want your identity disclosed to the manufacturer, place an "x" in this box. ☐

## Procedure for Compensation

The investigator shall report all serious and unexpected adverse events to the licensing authority, the sponsor and the ethics committee, within 24 hours of the occurrence of the events.

I. In Case of Trial Related Death

II. In Case of Trial Related Injury and SAE

## Compensation Formula

Compensation Formula for SAE or Death

$$\text{Compensation Formula} = \frac{B \times F \times R}{99.37}$$

- Computing the 3 factors viz.
- a) Age
- b) Risk and
- c) base amount

- B = Base amount (i.e. 8 lakhs)
- F = Factor depending on the age of the subject (based on Workmen Compensation Act)
- R = Risk Factor depending on the seriousness and severity of the disease - scale of 0.5 to 4
- Compensation amount will vary from a minimum of Rs. 8 lakhs to a maximum of Rs. 73.60 lakhs depending on the sage of the deceased and the risk factor.

### Trial related SAE causing permanent Disability to the subject

Compensation = (D x 90 x C) / 100*100

- D = % of Disability
- C = Quantum of Death compensation as calculated above

### Trial related SAE causing Life-threatening Disease

Compensation = N*W

- N = No of days the subject under life threatening Situation requiring medical care, irrespective of number of days of hospitalization
- W = Minimum Wages per day of Unskilled worker (in Delhi)

### Trial related SAE causing congenital Anomaly or Birth Defect

- Quantum of compensation will be calculated with half base amount ie., 4 lacs

Compensation = {(B/2) x F x R} / 99.37

### Limitation

- No compensation should be paid for the failure of a medicinal product to have its intended effect or to provide any other benefit to the patient.
- No compensation should be paid for injury caused by other licensed medicinal products administrated to the patient for the purpose of comparison with the product under trial
- No compensation should be paid to patients receiving placebo in consideration of its failure to provide a therapeutic benefit

- No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen:
  - through a significant departure from the agreed protocol
  - through the wrongful act or default of a third party, including a doctor's failure to
  - deal adequately with an adverse reaction
  - through contributory negligence by the patient

## Tool to Calculate Compensation


### Tool to Calculate Compensation

CDSA aims to build capacity and capability in the area of clinical development and translational research. To aid, promote, conduct of pre-clinical and clinical product development in India, CDSA undertakes and implement cost-effective clinical re semi-government, academic institutions, non-profit and small and medium sized enterprises.

To achieve our mandate, we are committed to provide essential and valued resource for professionals and researchers in the

CDSCO has devised a formula to determine the quantum of compensation in the cases of Clinical Trial-related SAEs (deaths ar

To calculate the quantum of compensation CDSA has developed "Tool to Calculate Quantum of Compensation" which calculate the compensation.

- Guide to Use Excel Sheet
- Quantum of Compensation

http://cdsaindia.in/tool-calculate-compensation

## What? When? Who? How? and Whom? of SAE Reporting

| What? | Who to Whom? | | | When? | | | How? |
|---|---|---|---|---|---|---|---|
| All SAEs during clinical trial | Investigator | Sponsor | EC | Investigator | Sponsor | EC | Appendix-XI format |
| | DCGI<br>EC<br>Head of Institution<br>Sponsor | DCGI, EC, Head of Institution | DCGI | Initial: <24hrs | Full report: within 10/14 days | ≤10 days/ 14 days | ≤21/ 30 days |

# ADVERSE DRUG REACTION REPORTING FORMS

by

**Ms. S. Devipriya,**
**Patent Safety, Pharmacovigilance Associate –**
**Pharmacovigilance Programme of India (PvPI), Madras Medical College, Chennai**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Agenda

- Pharmacovigilance Program of India (PvPI)
  - modes of ADR reporting with an emphasis on sADR reporting form
- Haemovigilance Program of India (HvPI)
  - Transfusion Reaction Reporting Form (TRRF)
- Adverse Event Following Immunization (AEFI)
  - AEFI notification form
- Materiovigilance Program of India (MvPI)
  - Medical Device Adverse event reporting form(MDAE reporting form)

## Pharmacovigilance Program of India (PvPI)

PvPI was initiated by Govt. of India in

- July 2010 with AIIMS, New Delhi as NCC (National Coordination center) for monitoring ADRs in the country
- NCC was shifted from AIIMS, New Delhi to IPC (Indian Pharmacopoeia Commission), Ghaziabad on 15th April 2011

## PvPI...

- Spontaneous and Voluntary reporting of adverse drug reactions (ADRs) by healthcare professionals
- 210 Medical Institutions including Corporate hospitals are involved in reporting ADRs through VIGIFLOW

MMC is one of the ADR Monitoring Center (AMC/Pharmacovigilance Center) under PvPI

## PvPI...

- Monitors ADRs among Indian Population
- Recommends CDSCO for regulatory decision
- Collaborates with WHO-UMC (Uppsala Monitoring Center)
- – Sends Individual Case Safety Reports (ICSRs)through VIGIFLOW (online safety data management system)

## PvPI…

Modes of ADR reporting – PvPI

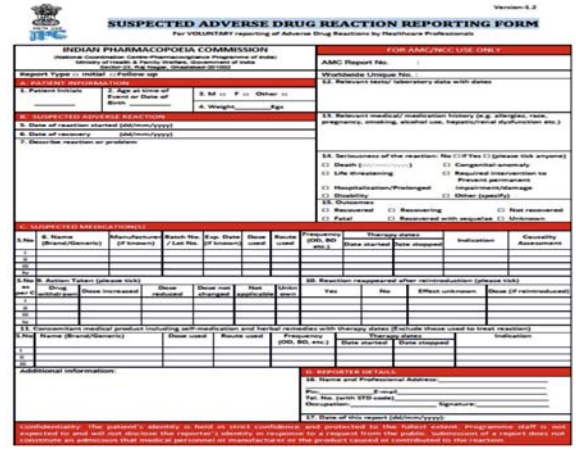
1. PvPI help line (toll free):
   9am -5:30pm, Monday-Friday

2. PvPI ADR android mobile app
   – report ADRs anywhere anytime (download from google play store)

3. By using Suspected Adverse Drug Reaction Reporting Form (sADR reporting form)

1800-180-3024

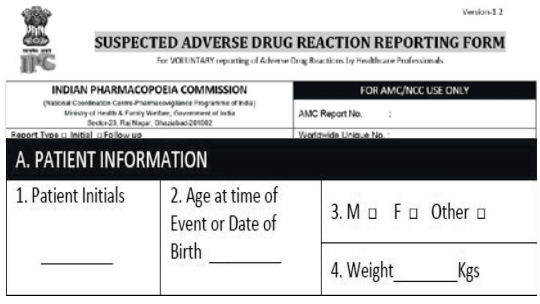

## sADR reporting form-PvPI


SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

## Basic components of sADR reporting form

### A. Patient Information

- 1.*Patient initials
- 2.*Age at time of event or date of birth: Write either the date of birth or age of the patient.
- 3.*Sex
- 4.Weight & height


SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

INDIAN PHARMACOPOEIA COMMISSION

FOR AMC/NCC USE ONLY

A. PATIENT INFORMATION

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

## Basic components of sADR reporting form

### B. Suspected Adverse Reaction

5. *Date of reaction started: Mention the date on which the reaction was first observed.
6. *Date of recovery: If the reaction recovered, the date on which the patient recovered from the reaction should be reported.
7. *Describe reaction: Provide the description of the reaction in terms of nature, localization

Ex: For example patient developed erythematous maculopapular rash with itching over upper and lower limb.

| B. SUSPECTED ADVERSE REACTION |
|---|
| 5. Date of reaction started (dd/mm/yyyy) |
| 6. Date of recovery (dd/mm/yyyy) |
| 7. Describe reaction or problem |

## Basic components of sADR reporting form

**C. Suspected Medications**

8. *The details of suspected medication(s) such as drug name (brand or generic name),

- manufacturer
- batch no/lot no
- expiry date

Mandatory if the ADR is life threatening or causing death

- *dose & frequency used
- *route used
- *dates of therapy started and stopped
- *and indication for which the drug is given

## Basic components of sADR reporting form

**C. Suspected Medications**

**9. *Action taken (Dechallenge details):**

Mention the status as:

Drug withdrawn  Dose reduced
Dose not Changed  Not applicable
Unknown

**10. * Reaction reappeared after reintroduction (Rechallenge details):**

Mention the status as:

Yes  No  Effect unknown
Not applicable
Dose (if reintroduced)

## sADR reporting form-PvPI

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 | | | | | | | |

## Basic components of sADR reporting form

11. Concomitant drugs: Write the details of all concomitant drugs including self medication,OTC medication, herbal remedies with therapy dates.

12. Relevant tests/ laboratory data: Mention all laboratory data relevant to the reaction occurred.

13. Relevant medical/medication history: Write the relevant history persistent to patient including preexisting medical conditions

(e.g. allergies, pregnancy, smoking, alcohol use, hepatic/renal dysfunction) and concurrent conditions.

## Basic components of sADR reporting form

14. *Seriousness of the reaction:
Yes No

If Yes please tick anyone
Death - if the patient died due to ADR

Life-threatening - patient is at substantial risk of dying at the time of the ADR

Hospitalisation/prolonged - due to ADR

Disability'- if adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions

## Basic components of sADR reporting form

Congenital anomaly - if exposure of drug prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required intervention to prevent permanent impairment/damage-if medical / surgical intervention was necessary to preclude permanent impairment

Other -event does not fit above conditions

## Basic components of sADR reporting form

**15. *Outcome of the patient**
- Recovered
- Recovering
- Fatal
- Continuing
- Unknown

### sADR reporting form-PvPI

12. Relevant tests/ laboratory data with dates

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

## Basic components of sADR reporting form

Treatment given for the reaction (Additional Information)
- Yes No Unknown

If Yes, Specify the treatment given for the ADR
1.---------
2.---------

**D. *Reporter Details**
**16. Name & Professional address :**
- *Reporter's Name
- *Designation
- *Signature with Date
- Address, E-mail ID & Phone number

**17. Date of the report (dd/mm/yyyy)**

## sADR reporting form-PvPI

| Additional Information: | D. REPORTER DETAILS |
|---|---|
| | 15. 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.

## Hamovigilance Program of India (HvPI)

Haemovigilance is a process of data collection and analysis of transfusion-related adverse reactions in order to investigate their causes and outcomes and prevent their occurrence or recurrence.

- HvPI was launched on 10th Dec 2012 by IPC as integral part of PvPI
- National Institute of Biologicals (NIB) is the NCC for HvPI
- NIB collates & analyze adverse reaction data for blood and blood products

## HvPI- Transfusion Reaction Reporting Form (TRRF)

National Institute of Biologicals
Ministry of Health & Family Welfare, Govt. of India
(National Coordinating Center)
HAEMOVIGILANCE PROGRAMME OF INDIA

Transfusion Reaction Reporting Form (TRRF) For Blood & Blood Components & Plasma Products

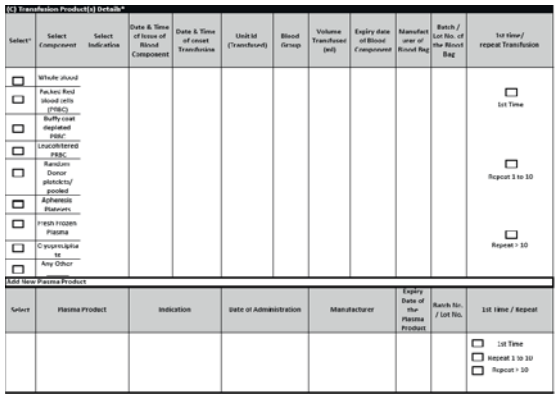
* Mandatory Field

| (A) Patient information | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hospital Code No.: | | | | | | | |
| Patient Initials*: | Gender*: | Blood Group*: | | | | | |
| Hospital Admission No.*: | Age/Date of Birth*: | ____Yrs | ____Month | ____Days | ____Hrs | ____Mins | |
| Primary Diagnosis*: | | | | | | | |
| Medical History: | | | | | | | |

## HvPI- Transfusion Reaction Reporting Form (TRRF)

| (B) Transfusion Reaction Details* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Was the patient under anaesthesia during transfusion: Yes/No If Yes type : GA/Spinal/LA | | | | | | | | | | | |
| Pre-transfusion Vitals: | | | | | | | Temp: | Pulse: | BP: | RR: | SPO2: |
| Vitals at the time of reaction: | | | | | | | Temp: | Pulse: | BP: | RR: | SPO2: |
| Please tick mark the relevant signs and symptoms listed below | | | | | | | | | | | |
| Generalised | | Pain | | Respiratory | | Renal | | Circulatory | | | |
| ☐ Fever | ☐ Anxiety | ☐ Chest Pain | | ☐ Dyspnoea | | ☐ Haematuria | | ☐ Tachycardia | | | |
| ☐ Chills | ☐ Itching (Pruritus) | ☐ Abdominal | | ☐ Wheeze | | ☐ Haemoglobinuria | | ☐ Hypertension | | | |
| ☐ Rigors | ☐ Edema (Site)___ | ☐ Back/Flank Pain | | ☐ Cough | | ☐ Oliguria | | ☐ Hypotension | | | |
| ☐ Nausea | ☐ Juandice | ☐ Infusion Site Pain | | ☐ Hypoxemia | | ☐ Other_____ | | ☐ Raised JVP | | | |
| ☐ Urticaria | ☐ Other____ | ☐ Other____ | | ☐ | | | | ☐ Arrhythmias | | | |
| ☐ Flushing | | | | ☐ Bilateral Infiltrates on | | | | ☐ Other___ | | | |
| ☐ Restlessness | | | | Chest X-ray | | | | | | | |
| ☐ Vomiting | | | | ☐ Other_____ | | | | | | | |
| Any Other(Specify): _____ | | | | | | | | | | | |

## HvPI- Transfusion Reaction Reporting Form (TRRF)



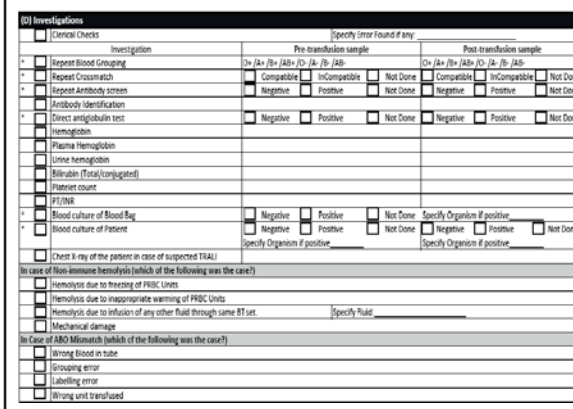
(C) Transfusion Product(s) Details*

| Select* | Select Component | Select Indication | Date & Time of Issue of Blood Component | Date & Time of onset of Transfusion | Unit Id (Transfused) | Blood Group | Volume Transfused (ml) | Expiry date of Blood Component | Manufacturer of Blood Bag | Batch / Lot No. of the Blood Bag | 1st time/ repeat Transfusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | Whole Blood | | | | | | | | | | ☐ 1st Time |
| ☐ | Packed Red Blood cells (PRBC) | | | | | | | | | | |
| ☐ | Buffy coat depleted PRBC | | | | | | | | | | |
| ☐ | Leucofiltered PRBC | | | | | | | | | | ☐ Repeat 1 to 10 |
| ☐ | Random Donor platelets/ pooled | | | | | | | | | | |
| ☐ | Apheresis Platelets | | | | | | | | | | |
| ☐ | Fresh Frozen Plasma | | | | | | | | | | ☐ Repeat > 10 |
| ☐ | Cryoprecipitate | | | | | | | | | | |
| ☐ | Any Other | | | | | | | | | | |

Add New Plasma Product

| Select | Plasma Product | Indication | Date of Administration | Manufacturer | Expiry Date of the Plasma Product | Batch No. / Lot No. | 1st time / Repeat |
|---|---|---|---|---|---|---|---|
| | | | | | | | ☐ 1st Time ☐ Repeat 1 to 10 ☐ Repeat > 10 |

## HvPI- Transfusion Reaction Reporting Form (TRRF)



(D) Investigations

☐ Clinical Checks — Specify Error Found if any: _____

| | Investigation | Pre-transfusion sample | Post-transfusion sample |
|---|---|---|---|
| * ☐ | Repeat Blood Grouping | /O+ /A+ /B+ /AB+ /O- /A- /B- /AB- | /O+ /A+ /B+ /AB+ /O- /A- /B- /AB- |
| * ☐ | Repeat Crossmatch | ☐ Compatible ☐ InCompatible ☐ Not Done | ☐ Compatible ☐ InCompatible ☐ Not Done |
| * ☐ | Repeat Antibody screen | ☐ Negative ☐ Positive ☐ Not Done | ☐ Negative ☐ Positive ☐ Not Done |
| ☐ | Antibody Identification | | |
| * ☐ | Direct antiglobulin test | ☐ Negative ☐ Positive ☐ Not Done | ☐ Negative ☐ Positive ☐ Not Done |
| ☐ | Hemoglobin | | |
| ☐ | Plasma Hemoglobin | | |
| ☐ | Urine hemoglobin | | |
| ☐ | Bilirubin (Total/conjugated) | | |
| ☐ | Platelet count | | |
| ☐ | PT/INR | | |
| * ☐ | Blood culture of Blood Bag | ☐ Negative ☐ Positive ☐ Not Done | Specify Organism if positive_____ |
| * ☐ | Blood culture of Patient | ☐ Negative ☐ Positive ☐ Not Done | ☐ Negative ☐ Positive ☐ Not Done |
| | | Specify Organism if positive_____ | Specify Organism if positive_____ |
| ☐ | Chest X-ray of the patient in case of suspected TRALI | | |

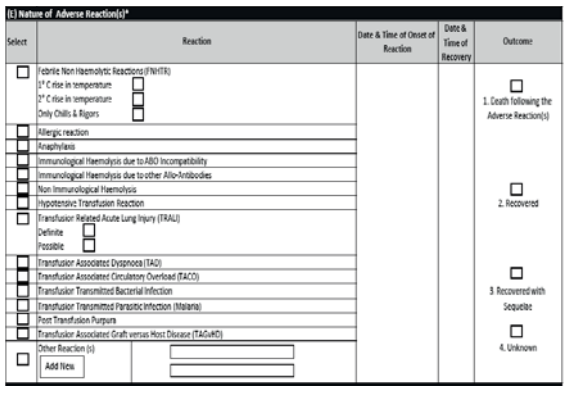
In case of Non-immune hemolysis (which of the following was the case?)

☐ Hemolysis due to freezing of PRBC Units
☐ Hemolysis due to inappropriate warming of PRBC Units
☐ Hemolysis due to infusion of any other fluid through same BT set. — Specify Fluid _____
☐ Mechanical damage

In Case of ABO Mismatch (which of the following was the case?)

☐ Wrong Blood in tube
☐ Grouping error
☐ Labelling error
☐ Wrong unit transfused

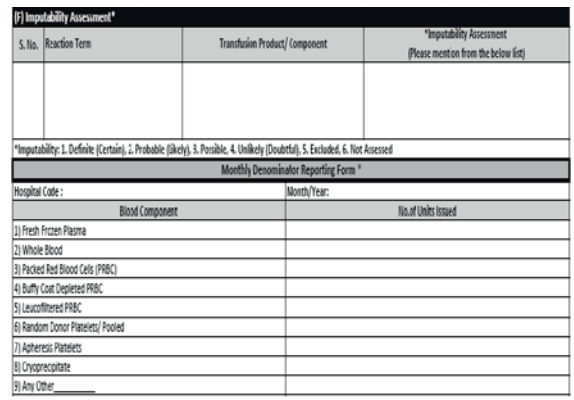
## HvPI- Transfusion Reaction Reporting Form (TRRF)



(E) Nature of Adverse Reaction(s)*

| Select | Reaction | Date & Time of Onset of Reaction | Date & Time of Recovery | Outcome |
|---|---|---|---|---|
| ☐ | Febrile Non Haemolytic Reactions (FNHTR)<br>1° C rise in temperature ☐<br>2° C rise in temperature ☐<br>Only Chills & Rigors ☐ | | | ☐ 1. Death following the Adverse Reaction(s) |
| ☐ | Allergic reaction | | | |
| ☐ | Anaphylaxis | | | |
| ☐ | Immunological Haemolysis due to ABO Incompatibility | | | |
| ☐ | Immunological Haemolysis due to other Allo-Antibodies | | | |
| ☐ | Non Immunological Haemolysis | | | ☐ 2. Recovered |
| ☐ | Hypotensive Transfusion Reaction | | | |
| ☐ | Transfusion Related Acute Lung Injury (TRALI)<br>Definite ☐<br>Possible ☐ | | | |
| ☐ | Transfusion Associated Dyspnoea (TAD) | | | |
| ☐ | Transfusion Associated Circulatory Overload (TACO) | | | ☐ 3. Recovered with Sequelae |
| ☐ | Transfusion Transmitted Bacterial Infection | | | |
| ☐ | Transfusion Transmitted Parasitic Infection (Malaria) | | | |
| ☐ | Post Transfusion Purpura | | | |
| ☐ | Transfusion Associated Graft versus Host Disease (TAGvHD) | | | ☐ 4. Unknown |
| ☐ | Other Reaction (s) Add New | | | |

## HvPI- Transfusion Reaction Reporting Form (TRRF)



(F) Imputability Assessment*

| S. No. | Reaction Term | Transfusion Product/ Component | *Imputability Assessment (Please mention from the below list) |
|---|---|---|---|
| | | | |

*Imputability: 1. Definite (Certain), 2. Probable (likely), 3. Possible, 4. Unlikely (Doubtful), 5. Excluded, 6. Not Assessed

Monthly Denominator Reporting Form *

| Hospital Code : | Month/Year: |
|---|---|
| Blood Component | No.of Units Issued |
| 1) Fresh Frozen Plasma | |
| 2) Whole Blood | |
| 3) Packed Red Blood Cells (PRBC) | |
| 4) Buffy Coat Depleted PRBC | |
| 5) Leucofiltered PRBC | |
| 6) Random Donor Platelets/ Pooled | |
| 7) Apheresis Platelets | |
| 8) Cryoprecipitate | |
| 9) Any Other_____ | |

## Adverse Event following Immunization (AEFI)

AEFI is defined as a medical event that takes place after immunization.

AEFI surveillance -

- monitors immunization safety
- detects and responds to adverse events
- corrects unsafe immunization practices
- reduces the negative impact of the event on health

The division of AEFI, Ministry of Health and Family Welfare, Government of India and PvPI monitors the safety of vaccines

## AEFI...

AEFI cases can be reported to:

AMC/NCC – PvPI

↓

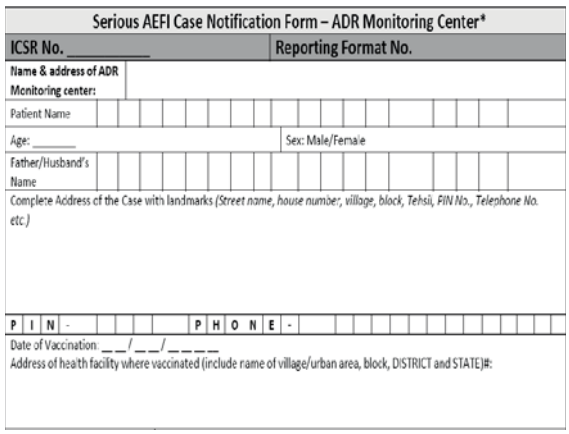
National level AEFI committee & State Expanded Programme Immunization Officers (SEPIO)

↓

AEFI committee follows with local AEFI team to completely furnish FIR/PIR/DIR to do the causality assessment

FIR: First Information report form
PIR: Preliminary Investigation report form
DIR: Detailed investigation report form

## PvPI - AEFI Notification form



Serious AEFI Case Notification Form – ADR Monitoring Center*

ICSR No. _____ | Reporting Format No.

Name & address of ADR Monitoring center:

Patient Name

Age: _____ | Sex: Male/Female

Father/Husband's Name

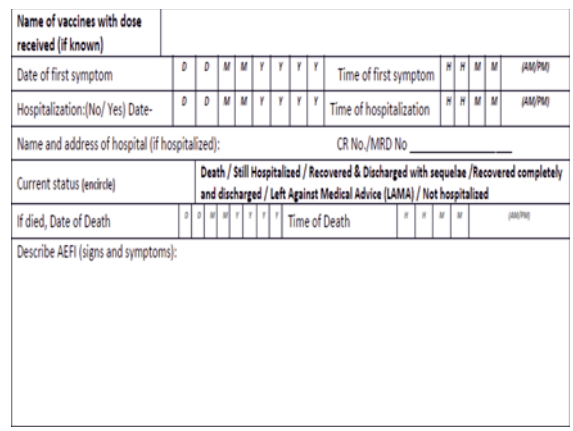
Complete Address of the Case with landmarks (*Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.*)

PIN - PHONE -

Date of Vaccination: __/__/____

Address of health facility where vaccinated (include name of village/urban area, block, DISTRICT and STATE)#:

## PvPI - AEFI Notification form



| | | | |
|---|---|---|---|
| Name of vaccines with dose received (if known) | | | |
| Date of first symptom | D D M M Y Y Y Y | Time of first symptom | H H M M (AM/PM) |
| Hospitalization:(No/ Yes) Date- | D D M M Y Y Y Y | Time of hospitalization | H H M M (AM/PM) |
| Name and address of hospital (if hospitalized): | | CR No./MRD No _____ | |
| Current status (encircle) | Death / Still Hospitalized / Recovered & Discharged with sequelae /Recovered completely and discharged / Left Against Medical Advice (LAMA) / Not hospitalized | | |
| If died, Date of Death | D D M M Y Y Y Y | Time of Death | H H M M (AM/PM) |
| Describe AEFI (signs and symptoms): | | | |

## PvPI - AEFI Notification form

| |
|---|
| Name & Signature of Nodal Officer:<br><br>Email:<br>Contact No. |
| *Date form sent to District Immunization Officer# (**where patient was vaccinated**)- __/__/____ |
| *Date form sent to State Immunization Officer# (**where patient was vaccinated**)- __/__/____ |
| *Date form sent to PVPI, Ghaziabad- __/__/____ |
| *Date form sent to Immunization Division / AEFI Secretariat (aefiindia@gmail.com)-__/__/____ |
| Name & signature of Technical Assistant (person filling this form):<br><br>E mail:<br>Contact number: |

#The case is to be notified to the DIO of the district where the vaccine was administered.
*This form should be scanned and emailed simultaneously to DIO, SEPIO, PVPI and AEFI Secretariat.

## Materiovigilance Program of India (MvPI)

**MvPI**

- Launched on 06th July 2015 at IPC, Ghaziabad by DCG(I)
- Monitors the safety of medical devices in the country
- IPC is National Coordination Center (NCC)
- Sree Chitra Tirunal Institute of Medical Sciences & Technology (SCTIMST) will be function as National Collaborating Centre

## Medical Device Adverse Event reporting form (MDAE reporting form)

**MEDICAL DEVICE ADVERSE EVENT REPORTING FORM**
**Materiovigilance Programme of India**

| FOR MDMC/NCC USE ONLY | |
|---|---|
| Type of report: Initial ☐ Follow-up ☐ | Report No. : |
| **A. PATIENT DETAILS** | |
| 1. Patient Hospital ID ---------- | 3. Age at time of Event or Date of Birth _____ |
| 2. Sex: M ☐ F ☐ | 4. Weight (Kg)_____ |
| **B. EVENT DETAILS** | |
| 1. Event description- | |
| Reason for the Event(Tick) a) Electrical ☐ b) Mechanical ☐ c) Electronic ☐ d) Biocompatibility ☐ e) Clinical application error ☐ | |

## Medical Device Adverse Event reporting form (MDAE reporting form)

2. Severity of the event (Yes ☐ No ☐) if yes please specify following
☐ Death (---/---/-------) ☐ cause congenital-anomaly ☐ Life threatening ☐ Required intervention to prevent death or impairment of body function
☐ Hospitalization/Prolonged impairment/damage ☐ Disability ☐ Other (specify).....
3. Date of event - (dd/mm/yyyy)
4. Location of the event- OPD ☐ IPD ☐ Others(Please specify).....
5. Device category: (A) Therapeutic ☐ Diagnostics ☐ Both ☐ (B) Implantable device ☐ Non Implantable device ☐
(C). Single use device ☐ Reusable device ☐ Reuse of manufacture marked single use device ☐
6. Date-

| Last preventive maintenance | Last calibration |
|---|---|
| | |

7. Location of device after the incident:
Place of use ☐ Place of reporter ☐ Place of Manufacture/vendor ☐ With patient or end user ☐
8. Is device in use after incident Yes ☐ No ☐
9. (A) Is same model device available in organisation? Yes ☐ No ☐ If yes, Quantity.....
(B) Organization - Healthcare facility ☐ Manufacturer ☐

## Medical Device Adverse Event reporting form (MDAE reporting form)

| C. MEDICAL DEVICE(S) DETAIL | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Name of Medical Device (1) | Manufacturer (2) | Brand Name (3) | Model No. (4) | Serial No. (5) | Batch No./ Lot No. (6) | Catalogue No. (for instruments only) | Date of installation/ implantation/ explantation (8) | List of Accessories (9) |
| | | | | | | | | |

| 10. Actions taken immediately after incident | 11. A Whether other medical devices were being used at same time with above device for therapeutic of diagnostic service? If yes, please specify.....<br><br>11 B. Any history of adverse event(s) from device with same serial/model/catalogue number. If yes please specify..... |
|---|---|

## Medical Device Adverse Event reporting form (MDAE reporting form)

| D.REGULATORY DETAILS | | | E. REPORTER DETAILS of MvPI CENTRE |
|---|---|---|---|
| Manufacturer name:<br><br>Regulator in Country of origin:<br><br>Regulatory status in origin country: | Entity legally representing the Manufacture:<br><br>Country: | Notified Body name in:<br><br>(I) Country of Manufacturing :<br><br>(II) In India: | Name and Professional Address:_____<br>_____Pin:_____ E-mail_____<br>Tel. No. (with STD code)_____<br>Designation:_____<br>Signature:_____<br>Date of this report___dd/mm/yyyy |

**F. Causality Assessment Details** Completed ☐ In Progress ☐ Awaited ☐

Additional Information:

**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 adverse event.**

# Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products

Effective from January 2018
Published by
Indian Pharmacopoeia Commission
National Coordination Centre – Pharmacovigilance Programme of India

For more information please visit the below link
http://www.ipc.gov.in/PvPI/pub/Guidance%20Document%20for%20Marketing%20Authorization%20Holders.pdf

# ADR/AE AND ITS CLINICAL RELEVANCE

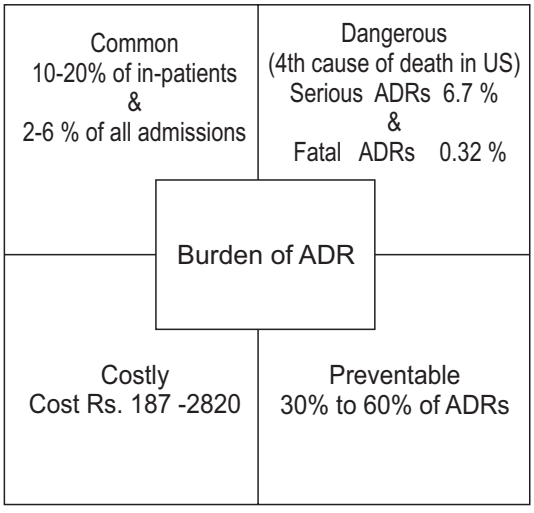
by

**Dr. A. Lourdu Jafrin,**
**Associate Professor& Head - Coordinator, ADR Monitoring Centre,**
**Dept. of Pharmacology, IGMC&RI**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## In this session….

- Introduction to ADR and AE
- Classification – overview
- Common ADRs & drugs implicated
- Clinical significance of ADRs and Role of HCP
- Management of ADRs
- Special group
- Learning Resources

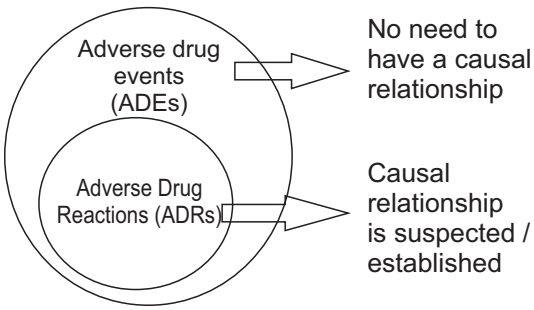



## Adverse event Vs ADR

- Any negative or harmful occurrence during treatment,
- may or may not be associated with a medicine.
- eg. Fall
- Temporal asson. +
- Causal relation +/-

- 'A response to a drug which is noxious and unintended, and which occurs at doses normally used… for the
- prophylaxis,
- diagnosis or
- therapy of disease, or
- for the modification of physiological function.'

## ADEs Vs ADRs



ADRs are classified based on

**Onset**

Acute (60 min), sub acute (1-24 hrs), latent (> 2 days)

**Severity**

Mild, moderate, severe & lethal

**Type**

Rawlins–Thompson classification

Immunologic and non-immunologic

## DoTS

| Dose relatedness | Time relatedness | Susceptibility |
|---|---|---|
| Toxic effects: high dose<br>Collateral effects: normal<br>Hypersusceptability reactions: low | Time-independent reactions: any time<br>Time-dependent reactions:<br>Rapid, early, intermediate, late, delayed | In some or continuous admin<br>Factors include: genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease. |

Beta blockers ⇨ Bradycardia,

Nitrates ⇨ Headache, Prazosin ⇨ Postural hypotension

Penicillin ⇨ Anaphylaxis

Phenytoin during pregnancy

Analgesics ⇨ Nephropathy

## Common drugs & ADRs

**ADR Incidence**

- Gastrointestinal tract events 22.1%
- Electrolyte/renal 16.7%
- Hemorrhagic 12.7%
- Metabolic/endocrine 9.5%

**Be vigilant with**

- Antibiotics
- Antineoplastics
- Cardiovascular drugs
- Hypoglycemics
- NSAID/Analgesics
- CNS drugs

**ADR manifestations:**
- Nausea, vomiting
- Change in bowel pattern
- Sedation
- Confusion, Giddiness
- Orthostatic hypotension

**Beta lactam antibiotics**
- Urticaria, anaphylaxis,
- Maculopapular rash
- Serum sickness
- SJS-TEN ( rare )

**Tetracyclines**
- Photosensitivity
- Pigmentation

**Sulphonamides**
- Hypersensitivity
- FDE
- EMF
- SJS-TEN ( rare )

**Quinolones**
- Anaphylactoid reaction
- Photosensitivity
- SJS-TEN
- Vasculitis
- Administration in children ?

**ATT**
- SJS-TEN
- EMF
- INH- LE like phenomenon
- Rifampicin- Drug induced pemphigus
- FDE
- Maculopapular rash
- Erythroderma

**Antileprosy drugs**
- Clofazimine – pigmentation
- Dapsone

FDE
EMF
DRESS
Erythroderma

**ART**
- Pigmentary changes
- Altered growth of hair and nails
- Maculopapular rash
- DRESS
- Exfoliative dermatitis
- Lipodystrophy
- Injection site reactions

**Antimalarials**
- Pigmentary changes
- Photosensitivity
- Precipitation of severe psoriasis
- Erythroderma
- Lichenoid eruptions, TEN

**NSAIDS**

- Urticaria
- Lichenoid rash
- Aggravated psoriasis
- FDE
- EMF,SJS,TEN
- Photosensitivity
- Exanthematous rash

**Antipsychotics**

- Pigmentation
- Lichenoid eruptions
- Erythema multiforme
- Phototoxicity
- LE like illness
- Erythroderma

**Anti epileptic drugs**

- FDE
- EMF SJS TEN
- DRESS
- Erythroderma
- Pseudolymphomas

**Cardiac drugs**

- Beta blockers- lichenoid eruptions , psoriasis
- Hydralazine – LE
- ACEI- urticaria
- Amiodarone- photosensitivity,onycholoysis

**CLINICAL CONSIDERATIONS**

**Suspect ADR ….**

- appears soon after a new drug is started
- after a dosage increase
- disappears when the drug is stopped
- reappears when a drug is restarted

**Who are at high risk for ADR?**

1. Polypharmacy
2. Irrational prescribing
3. Female gender
4. Co morbidity
5. Extremes of age
6. HIV infection, Alcoholism
7. Previous history
8. Specific genetic polymorphism

**FAQs**

- Medication history
  - Prescription medications, allergies or intolerances, adherence
- Intake of more than one drug, OTC, herbals, drug abuse
- Drug interaction - ADR
- Long term medication
- Time of onset
- Temporal relationship (onset, duration, frequency)
- End-organ function

**FAQs**

- Significant alteration of Lab values
- Social history
- Any other medical illness
- Demographics
  - age, race, ethnicity, gender, height, weight
  - Concurrent conditions or special circumstances
  - e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding

**Medication details….**

- Indication, dose, diluent
- Administration
  - Route, method, site, schedule, rate, duration
- Formulation
  - Pharmaceutical excipients
  - e.g., colorings, flavorings, preservatives
  - other components
  - e.g., DEHP, latex

**NO TEARS approach relevant to ADRs**

- *Need and indicatio*n
- Open questions
- Tests and monitoring
- Evidence and guidelines
- *Adverse effects*
- *Risk reduction and prevention*
- Simplification and switches

**Need and indication**

- Is the indication appropriate ?
- Is drug needed ?
- Is dose appropriate?
- Is the diagnosis been confirmed ?

**Adverse effects**

- Any side effects present ?
- Is side effect – prescription / OTC and complementary medicines?
- Are drugs prescribed for expected side effects ?
- Is there any new advice or warnings on side effects or interactions?

**Risk reduction and prevention**

- Social history & co morbidity.
- Is treatment optimised to reduce risks?

**Roles of health professionals**

1. Identifying and assessing ADRs
2. Preventing ADRs
3. Monitoring therapy
4. Explaining risks to patients

**1. Identifying and assessing ADRs**

- The temporal relationship
- The pharmacological plausibility
- Existing information in published drug information sources
- Concomitant medication
- Concurrent illness
- De / Re - challenge
- Previous medical history
- Potential for drug interactions

**2. Preventing ADRs**

- *88% of ADRs causing hospital admission in the elderly (Beijer and de Blaey, 2002)*
- *Drug interaction*
- *Inappropriate medication*
- *Unnecessary medication*
- *previous ADR history*

- minimising the use of drugs known to carry a high risk of ADRs and tailoring drug selection to individuals based on the factors which predispose them to ADRs.. For example, electronic decision support,

- increasing availability of guidance on drug selection and appropriate use should all increase rational prescribing,

**Preventable causes….**

- Medication errors?
- Intentional abuse or misuse?
- Intentional overdose?
- Unintended/occupational exposure?
- Drug quality problems?

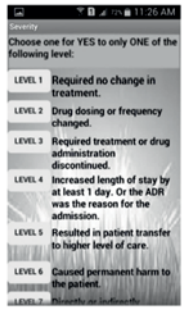
## Preventability scale

| | Item | Y | N |
|---|---|---|---|
| 1 | Was the drug involved in the ADR considered **not** considered **appropriate** for the patient's clinical condition? | Y | N |
| 2 | Was the **dose, route, and frequency** of administration **not appropriate** for the patient's age, weight and/or disease state? | Y | N |
| 3 | Were required **therapeutic drug monitoring** or other necessary laboratory tests not performed? | Y | N |
| 4 | Was there a history of **allergy or previous reactions** to the drug? | Y | N |
| 5 | Was a **drug interaction** involved in the reaction? | Y | N |
| 6 | Was a **toxic** serum level documented? | Y | N |
| 7 | Was **poor compliance** involved in the reaction? | Y | N |

## "Adverse Drug Rxn Preventability." android app



Apps "Adverse Drug Reaction Causality," "Adverse Drug Reaction Severity,"



## Avoid dangerous drug interactions

### Drug - Drug interaction

- Aspirin + Warfarin — Synergism (excessive bleeding)
- Decongestants + Antihypertensive — Potentiation (high blood pressure)
- Phenobarbital + Warfarin — Antagonism (less effect)
- Erythromycin + Warfarin — Synergism (increased bleeding)

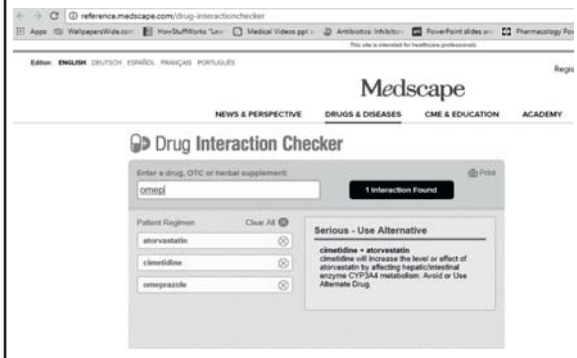
### Drug - Food interaction

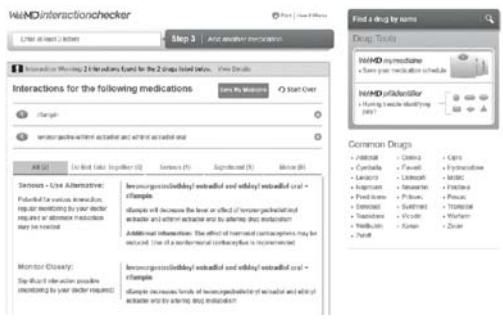
- Benzodiazepines + grapefruit
  Inhibit enzymes involved in drug metabolism
- Acetaminophen + Alcohol
  Liver damage
- MAO Inhibitors + food(tyramine)
  Severe headache
- Tetracycline's + calcium food
  Reduced absorption of drug

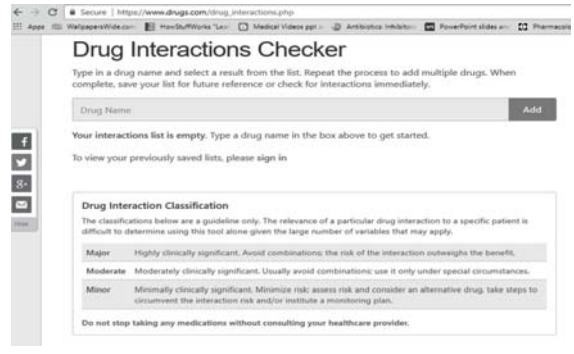
### Drug-Disease interaction

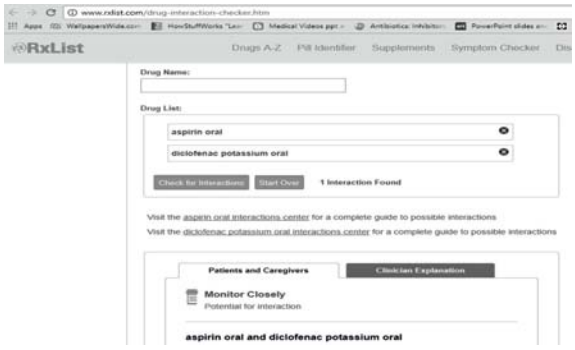
- Nasal decongestants+ Hypertension
  Increased blood pressure
- NSAID'S+ Asthmatic patients
  Air way obstruction
- Minoxidil+ Heart failure
  Fluid retention
- Calcium channel blocker + Heart failure
  Negative inotropic activity
- Beta blockers+ Heart failure
  Worsen asthma
- Metformin + Heart failure
  Increased lactate level


U.S. Department of Health and Human Services
FDA
U.S. FOOD & DRUG
ADMINISTRATION
Search FDA
Home
Food
Drugs
Medical Devices
Radiation-Emitting Products
Vaccines, Blood & Biologics
Animal & Veterina
Drugs
Home > Drugs > Drug Safety and Availability > Medication Errors
Medication Errors
Resources for You
Agency for Healthcare Research and Quality: Medical Errors and Patient Safety
Centers for Disease Control and Prevention: Medication Safety
Department of Veterans Affairs National Center for Patient Safety
Medication Errors Related to Drugs
SHARE
TWEET
LINKEDIN
PIN IT
EMAIL
PRINT
Within the Center for Drug Evaluation and Research (CDER), the Division of Medication Error Prevention and Analysis (DMEPA) reviews medication error reports on marketed human drugs including prescription drugs, generic drugs, and over-the-counter drugs. DMEPA uses the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) definition of a medication error. Specifically, a medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the


reference.medscape.com/drug-interactionchecker
Medscape
NEWS & PERSPECTIVE
DRUGS & DISEASES
CME & EDUCATION
ACADEMY
Drug Interaction Checker
Enter a drug, OTC or herbal supplement:
omepl
1 Interaction Found
Patient Regimen
Clear All
atorvastatin
cimetidine
omeprazole
Serious - Use Alternative
cimetidine + atorvastatin
cimetidine will increase the level or effect of atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.


WebMD interactionchecker
Step 3
Interactions for the following medications
Start over
Serious - Use Alternative:
Monitor Closely:
Find a drug by name
Drug Tools
WebMD mymedicine
WebMD pillidentifier
Common Drugs


Secure | https://www.drugs.com/drug_interactions.php
Drug Interactions Checker
Type in a drug name and select a result from the list. Repeat the process to add multiple drugs. When complete, save your list for future reference or check for interactions immediately.
Drug Name
Add
Your interactions list is empty. Type a drug name in the box above to get started.
To view your previously saved lists, please sign in
Drug Interaction Classification
The classifications below are a guideline only. The relevance of a particular drug interaction to a specific patient is difficult to determine using this tool alone given the large number of variables that may apply.
Major
Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate
Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.
Minor
Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.
Do not stop taking any medications without consulting your healthcare provider.

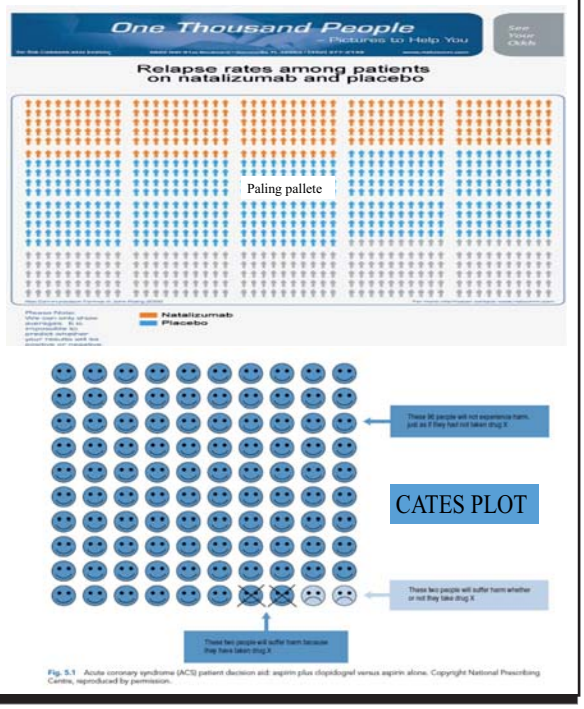



### 3. Monitoring therapy

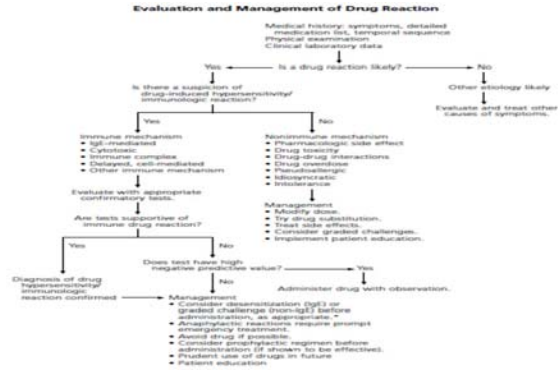
- *Direct*
  - *Renal and hepatic function & electrolytes*
  - *Cell counts*
- • *Physiological*

### 4. Explaining the risks vs benefit

- *Informed decision*
- *Discuss frequency of ADR*
  - *very common (1 in 10)*
  - *common (1 in 100)*
  - *very rare (1 in 10,000)*
- *Paling pallete and cates plot*




## Management of ADR



**Management of ADRs:**

- Discontinue the offending agent if:
  - it can be safely stopped
  - the event is life-threatening or intolerable
  - there is a reasonable alternative
- Continue the medication (modified as needed) if:
  - it is medically necessary
  - there is no reasonable alternative
  - the problem is mild and will resolve with time

**Management of ADRs:**

- *Discontinue non-essential medications*
- *Administer appropriate treatment*
  - *e.g., atropine, antihistamines, epinephrine, corticosteroids, glucagon etc*
- *Provide supportive or palliative care*
  - *e.g., hydration, glucocorticoids, warm / cold compresses, analgesics etc*
- *Consider desensitization*

**Management of ADRs:**

- **For dose-related ADRs:**
  - Modify the dose or reduce precipitating factors
- **For ADRs unrelated to dose:**
  - The drug usually should be withdrawn and re-exposure should be avoided.

**Teratology Information Services**

UK Teratology Information Service – Telephone and Online (TOXBASE) (http://www.uktis.org/)

European Network Teratology Information Services – (http://www.entis-org.eu/)

Organization of Teratology Information Specialists (http://parthenonmanagementgroup.com/portfolio/organization-of-teratology-information-specialists-otis/)


## ADRs in Children

- Admission - 0.4% to 10.3%
- ADRs during hospital admission – 0.6 – 16.8%
- ADRs in outpatient children – 0.07 – 11.01%
- Anti-infectives and anti-epileptics (in-patients)
- Anti-infectives and NSAIDs (out-patients)

Smyth RMD. PLoS ONE 2012;7:e24061

## Special population

| Age group | Drug | ADR | Mechanism |
|---|---|---|---|
| Newborns | Sulphonamide | Kernicterus | High affinity of drug for blood proteins displaces bilirubin |
| Newborns | Chloramphenicol | Gray baby syndrome | Impaired metabolism (UDP-gt, kidney) |
| Newborns and infants | Ceftriaxone – calcium solutions | Calcium precipitation (lungs) | Unknown |
| Infants and children | Sodium valproate | Hepatotoxicity | Abnormal metabolism (?) |
| Children | Propofol | Propofol infusion syndrome | Unknown – dose related |
| Children | Vigabatrin | Visual field defects | Unknown |
| Adolescents | Metoclopramide | Dystonia | Unknown |

## Elderly - considerations

- Body water reduced
- Adipose tissue increased
- Reduced linking power of drug to plasma proteins: Change of volume of distribution
- Reduced liver activity (i.e. reduced induction of enzymes)
- Reduced renal elimination
- Increased receptor sensibility
- Reduced efficiency of carrier proteins (reduced homeostasis)

Heckenbach K et al., Springerplus 2014;3:483

## Resources for reference

- Review drug labels
  - DailyMed, Drug@FDA
  - Safety Alerts – FDA, international
  - NLM – Livertox
  - Micromedex

# TRANSCRIPTION OF DATA CASE STUDY TO REPORTING FORM
## (Hands on Training)

by

**Mr. C. Stalin,**
**Patient Safety - Pharmacovigilance Associate (PVPI),**
**Adverse Events Monitoring Centre, Govt. Kilpauk Medical College & Hospital, Chennai.**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

### OVERVIEW OF THE PRESENTATION

How to fill

- ADR Reporting Form.
- Transfusion reaction reporting form (TRRF)
- Serious AEFI notification form.
- Medical device adverse event reporting form.

More New Drugs are being introduced into the country which include New Chemical Entities (NCE)

- New dosage forms
- New routes of drug administrations
- New therapeutic claims of existing drugs.
- It is important to monitor both the known and unknown effects of medicines in order to determine their safety profile.

### Case Study?

Case studies of individuals in health care research often involve

- in-depth interviews with participants
- key information
- review of the medical records
- observation.

### ICSR
### (Individual Case Safety Reports)

- Important in pre and post authorization of Drugs.
- All Serious reactions should be documented first.
- Documented as complete as possible.

### Who can Report?

- Investigators
- Health Care Professional's (HCP's)
- Patients / Non HCPs
- Health Authorities / License Partners, etc.

## Quality reporting of ICSRs

Valid Reports Should Have:

- Patient information: initials, age at onset of reaction, gender.
- Suspected adverse reaction:
- A reaction term(s)
- date of onset of reaction
- Suspected medication: Drug(s) name, dose, date of therapy started, indication of use, seriousness, outcome, de-challenge and re-challenge details
- Reporter: Name and address, causality assessment, date of report.

## Case Study - 1

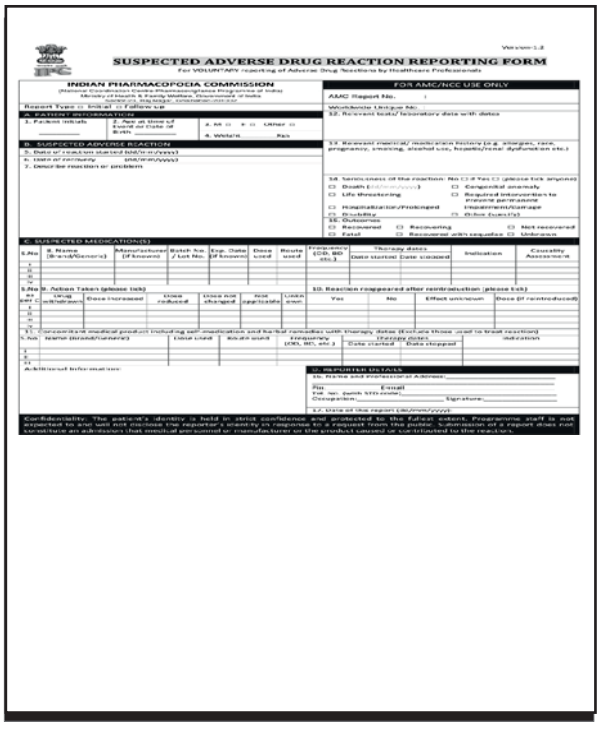
On 22/06/2016 Mr.KBL -A 38 years old, male patient presented to the emergency with chief complaints of rashes, oral ulceration and fever. When detailed history was taken, patient revealed onset of chief complaints from past 8 days beginning with fever Followed by rashes and difficulty in eating/swallowing due to oral ulcerations. Patient had previous history of pulmonary tuberculosis for which he had undergone treatment. Patient was diagnosed with General Tonic Clonic Seizures approximately 1 month back, for which he was prescribed Tab. Phenytoin 100 mg thrice a day from a local doctor. After 13 days of administration, patient developed fever for which he self-medicated with Tab. Paracetamol 500mg but with no effect. After 3 days patient started developing rashes beginning from trunk and progressing towards red eye. On physical examination, the patient as well-oriented, had hyperpyrexia, generalized, maculopapular rash all over the body and bullous eruptions on the neck, face and back. Ophthalmic examination showed acute conjunctivitis and sub conjunctival hemorrhages. Hemorrhagic ulcers over the eyelids were also noted. On general examination, BP was 110/80 mm of Hg, Pulse-94 beats/min, Respiratory rate- 16/min, chest auscultation and abdominal palpation did not reveal any significant finding. The patient was immediately admitted with diagnosis of drug induced Steven Johnson's Syndrome and Tab. Phenytoin and Tab. Paracetamol were immediately stopped. Patient was started with Intravenous fluids (1.5 liters/day), Intravenous Cefotaxime (1 gram every 12 hourly) for infection prophylaxis, Inj. Pheniramine Maleate 25 mg and inj. Prednisolone 10 mg qid. Oral ulcer was managed with the candid mouth paint and choline salicylate. Ofloxacin eye drops 0.3% was advised for eye lesion.

Patient started showing improvement after 2 days of treatment.Tab. Levetiracetam 500 mg bid was started from day 3rd as an alternative to Tab. Phenytoin and intravenous fluid was also stopped as patient was comfortable taking orally. Systemic steroid, Inj. Prednisolone 10 mg qid for 7 days, which was gradually tapered. Patient recovered completely after 22 days and was advised to continue Tab. Levetiracetam.

**Additional Information:** Phenytoin 100mg, Batch no: MK-03, Expiry date: 10/2017, Manufacturer: Hetero labs.

**Reporter:** Dr. PRQ , Asst.Professor, Dermatology dept, GKMC- Chennai-10.

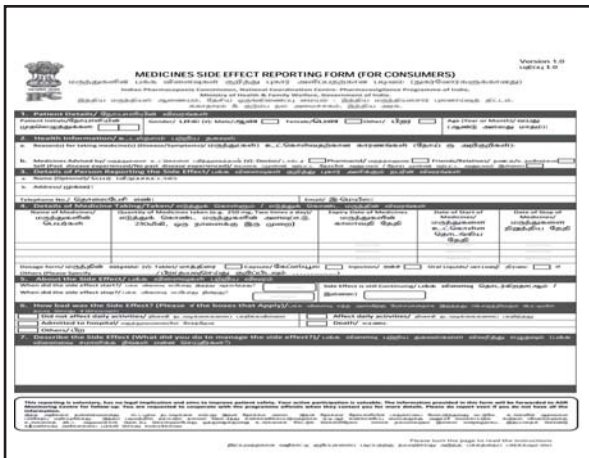
**Date of Report** : 15/08/2017.



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION



MEDICINES SIDE EFFECT REPORTING FORM (FOR CONSUMERS)

## Case Study 2

ALR- A 36 year old female trauma patient was taken for emergency surgery. A blood sample is received in the MRI blood bank for pre-transfusion testing, including type and antibody screen and crossmatch for six units of PRBCs. This testing was performed on an automated blood bank system and the cross matched units were issued to the operating room. Transfusion was started on 24/06/2017 at 1:50 pm. The patient received five units of packed RBCs during surgery. After infusion of 100mL of the sixth unit, the patient became hypotensive and the transfusion was stopped. Medical treatment was given and the patient's hypotension was resolved. The surgery was completed without additional transfusions. Following surgery, he was transported to the Surgical ICU for recovery. Soon after arriving in the ICU, hemoglobinuria is observed. This along with the drop in blood pressure during infusion of the sixth unit led the attending physician to suspect a transfusion reaction.

**Reporter:** Ms. Chitra Staff nurse, Blood bank GKM hospital- Chennai-10.

**Date of Report :** 15/08/2017.

Transfusion Reaction Reporting Form (TRRF) for Blood & Blood Products

Indian Pharmacopoeia Commission - National Institute of Biologicals
Ministry of Health & Family Welfare - Govt. of India
HAEMOVIGILANCE
(Pharmacovigilance Programme of India)

TRANSFUSION REACTIONS REPORTING FORM FOR BLOOD & BLOOD PRODUCTS

For reporting of transfusion reactions by Hospital/Transfusion Service

A) PATIENT INFORMATION * Mandatory Field

Patient initials* DOB/Age in years * Sex: * F M
Hospital Admission No: * Diagnosis Hospital Code No*
Date & Time of Transfusion * Date & Time of reaction* Date & Time of recovery

B) TRANSFUSION PRODUCT DETAILS*

| Components | Blood Components | Unit Number (transfused) | Expiry Date | Manufacturer | Batch Number | Indications | 1st time / Repeat Transfusion (No. of Repeats) |
|---|---|---|---|---|---|---|---|
| Whole Blood | | | | | | | |
| Red Blood Cells | | | | | | | |
| Platelets Concentrate | | | | | | | |
| Platelets Product PRP | | | | | | | |
| Solvent detergent (SD) Plasma | | | | | | | |
| Cryo | | | | | | | |
| Cryoprecipitate | | | | | | | |
| Any other Blood Products (Please Specify) | Manufacturer | | Batch Number | Expiry Date | | | |

C) NATURE OF ADVERSE REACTIONS *

| | Reactions | Please Tick (√) |
|---|---|---|
| 1 | Immunological Haemolysis due to ABO Incompatibility | |
| 2 | Immunological Haemolysis due to other alloantibodies | |
| 3 | Non Immunological Haemolysis | |
| 4 | Transfusion Transmitted Bacterial Infection | |
| 5 | Anaphylaxis / Hypersensitivity | |
| 6 | Transfusion Related Acute Lung Injury (TRALI) | |
| 7 | Transfusion Transmitted Viral Infection (HBV) | |
| 8 | Transfusion Transmitted Viral Infection (HCV) | |
| 9 | Transfusion Transmitted Viral Infection (HIV-1/2) | |
| 10 | Transfusion Transmitted Viral Infection, other (Specify) | |
| 11 | Transfusion Transmitted Parasitic Infection ( Malaria) | |
| 12 | Transfusion Transmitted Parasitic Infection, other (Specify) | |
| 13 | Post Transfusion Purpura | |
| 14 | Transfusion Associated Graft versus Host Disease (TAGVHD) | |
| 15 | Febrile Non Haemolytic Reactions(FNHTR) | |
| 16 | Transfusion Associated Dyspnea(TAD) | |
| 17 | Transfusion Associated Circulatory Overload (TACO) | |
| 18 | Other Reaction(s) | |

D) OUTCOMES OF THE ADVERSE REACTIONS*
- Death following the adverse reactions
- Recovered
- Recovered with sequelae
- Permanently disabled
- Unknown

E) REPORTER *
Name and professional Address:
PIN Code: Email:
Tel No. (with STD code):

F) CAUSALITY ASSESSMENT* Date of the report (DD/MM/YYYY)

Any other information

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## Case Study - 3

On 3 rd January 2017, ANW a 4-month-old male infant came to tertiary care teaching hospital. The infant was weighing around 4.75 kg . It as was observed that the infant was properly immunized for the age. Baby cried immediately after birth and developed social smile at 2 months. First dose of diphtheria, tetanus, pertussis (wholecell), hepatitis B (rDNA), and Haemophilus influenzae type B (Pentavac 0.5ml) and oral polio vaccine was administered on 5th week from the birth, and successively 2nd dose was immunized at the end of 9th week from the birth. No adverse event was reported. The baby was brought to the hospital for administering the third dose of immunization and immunized. While immunization the infant was crying with immediate micturition. But after 1 h following the immunization, reported with the following complaints: loose stools, up rolling of eyes, deviation of angle of mouth. In history, there were no similar complaints during the time of birth. On clinical examination infant showed, inactive, non-pallor, and cyanosis. Decreased cry activity with poor central nervous system reflux and tone was noted. 152 beats/min of heart rate with 40 beats/min respiratory rate was measured. Treatment was initiated after ruling out of seizure induced by other causes. No abnormal signs were observed from the computed tomography and MRI scan reports. Treatment was started immediately with intravenous (IV) isolate – P 475 ml/24 h, injection ceftriaxone 250 mg IV at 12th hourly, injection Vitamin K 2 mcg/day, syrup paracetamol (125 mg/5 ml), and hydration for 6 days and convulsions were monitored. After 2 days, the infant was alert, afebrile, active, heart rate was 136 beat/min with respiratory rate 44 beat/min. The patient was discharged on 3rd day. The discharge medication advice was provided. The event was reported to the DIO on 04/01/2017.

**Reporter:** Dr.Paras, Govt kilpauk medical college hospital- Chennai-10.

**Date of Report :** 04/01/2017.

Serious AEFI Case Notification Form – ADR Monitoring Center*

ICSR No. Reporting Format No.

Name & address of ADR Monitoring center (AMC):

Patient Name

Age: Sex: Male/Female

Father/Husband's Name

Complete Address of the Case with landmarks (Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)

PIN PHONE

Date of Vaccination: __/__/____

Address of health facility where vaccinated (include name of village/urban area, block, DISTRICT and STATE)#:

Name of vaccines with dose received (if known)

Date of first symptom Time of first symptom

Hospitalization (No/ Yes) Date- Time of hospitalization

Name and address of hospital (if hospitalized): CR No./MRD No

Current status (encircle) Death / Still Hospitalized / Recovered & Discharged with sequelae /Recovered completely and discharged / Left Against Medical Advice (LAMA) / Not hospitalized

If died, Date of Death Time of Death

Describe AEFI (signs and symptoms):

Name & signature of AMC Coordinator/ Medical officer:

Email:

Contact No.

*Date form sent to District Immunization Officer# (where patient was vaccinated): __/__/____

*Date form sent to State Immunization Officer# (where patient was vaccinated): __/__/____

*Date form sent to PVPI, Ghaziabad: __/__/____

*Date form sent to Immunization Division / AEFI Secretariat (aefindia@gmail.com): __/__/____

Name & signature of Pharmacovigilance Associate:

E mail:

Contact number:

#The case is to be notified to the DIO of the district where the vaccine was administered.

*This form should be scanned and emailed simultaneously to DIO, SEPIO, PVPI and AEFI Secretariat.

## Case Study - 4

This case was received from a health care professional regarding 80 year old male patient with a body weight of 68 kg, experienced arrhythmia due to pace maker programming. The reason for the event was marked as biocompatibility and the event occurred on 15/03/2017.The device category was implantable device and the last calibration was done on 11/Jan/2017. The location of the device after the incident was with in the patient and the device used after incident also. ECG was being used at same time with above device for therapeutic or diagnostic service.

**Medical device details:** name of device: Pacemaker, Manufacturer: St Jude medical, Model No: Endurity 2162, Serial no: 4745081 pr 17.01.39, Batch no: 120491173330v22.0, and the regulator country was USA.

Reporter Details: Dr Alben Sugamani, Department of clinical research, Anekal, Bommasandra, Karnataka, 560099.

MEDICAL DEVICE ADVERSE EVENT REPORTING FORM

Materiovigilance Programme of India

FOR MDMC/NCC USE ONLY

Type of report: Initial / Follow up(s) Report No:

A. PATIENT DETAILS

1. Patient Hospital ID 2. Age at time of Event or Date of Birth

3. Sex: M / F / O 4. Weight (kg)

B. EVENT DETAILS

1. Event description

2. Reason for the Event(Tick) a) Electrical b) Mechanical c) Electronic d) Biocompatibility e) Clinical application error

3. Seriosity of the event Yes / No / If yes please specify following

i) Death (…/…/……) ii) cause congenital anomaly iii) Life threatening iv) Required intervention to prevent death or impairment of body

v) Hospitalization/Prolonged impairment/damage vi) Disability vii) Other (specify)

4. Date of event

5. Device related to event GPI / IPD / Others(Please specify)

6. Device category: (A) Therapeutic / Diagnostic / Both / (B) Implantable device / Non implantable device

(C) Single use device / Reusable device / Reuse of manufacture marked single use device

7. Date: Last preventive maintenance Last calibration

8. Location of device after the incident:

Place of use / Place of inspection / Place of Manufacture/vendor / With patient or end user

9. (A) Is same model device available in organization? Yes / No / If yes, Quantity:

(B) Organization: Healthcare facility / Manufacturer /

C. ANTICIPATED DEVICE DETAILS

| Name of Medical Device | Manufacturer | Brand Name | Model No. | Serial No. | Batch No./ Lot No. | Catalogue No. (For instruments only) | Date of implantation/ explantation | Last of Acknowledge |
|---|---|---|---|---|---|---|---|---|
| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) |

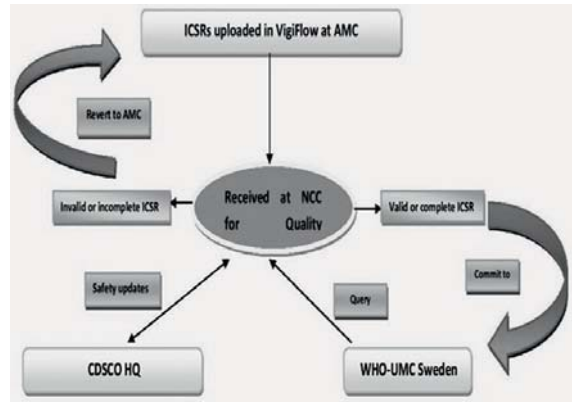
10. Actions taken immediately after incident

11. A Whether other medical devices were being used at same time with above device for therapeutic or diagnostic service? If yes, please specify

11 B. Any history of adverse events from device with same serial/model/catalogue number, if yes please specify

Page 1 of 2

## Processing Of ADR Reports



# LOGISTIC METHODOLOGY OF CAUSALITY OF ASSESSMENT

by

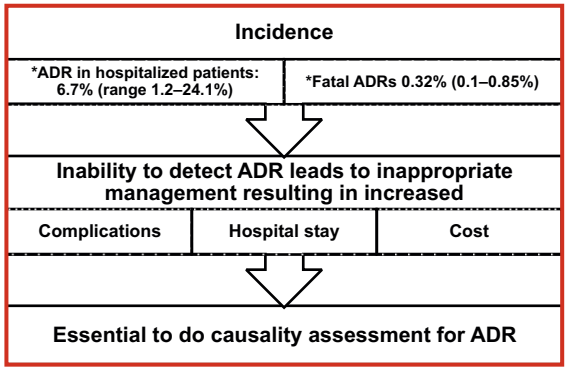
**Dr. S. Sandhiya,**
**Assistant Professor & AMC Co-ordinator,**
**Department of Clinical Pharmacology, JIPMER, Puducherry**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Overview

- Introduction
- Causality assessment
  - Definition & importance
- Methods of causality assessment
  - Probabilistic/ logistic methods
- Group exercises

## Introduction

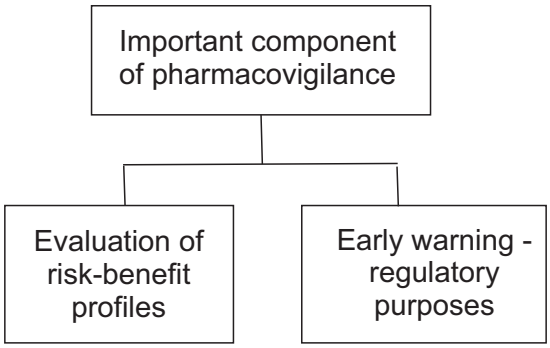



## Causality assessment - Definition

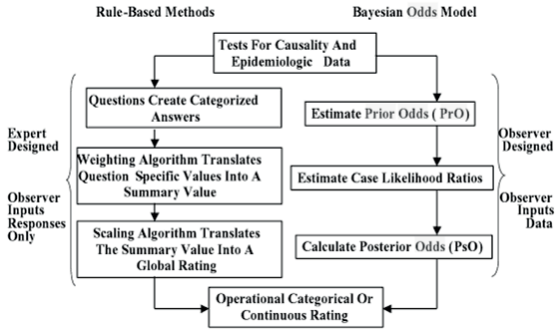
Causality assessment is the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event.

It assesses relationship between drug treatment & occurrence of adverse event.

## Causality assessment - Importance



## Methods of Causality Assessment




## Methods of Causality Assessment

| | |
|---|---|
| Expert judgement | • assessments based on previous knowledge & experience in the field<br>• Eg. WHO–UMC causality scale |
| Algorithms | • set of specific questions with scores to calculate cause-effect relationship<br>• Eg. Naranjo's algorithm |
| Probabilistic/ logistic (Bayesian approaches) | • Use specific findings in a case to alter prior estimate of probability into posterior estimate of probability of causation<br>• Eg. Bayesian Adverse Reactions Diagnostic |

## Expert Judgement

| WHO–UMC scale | |
|---|---|
| Time relationship (between drug use & ADR) | Certain |
| Absence of other causes (drugs/disease) | Probable |
| Dechallenge | Possible |
| | Unlikely |
| Rechallenge | Unclassified |
| | Unclassifiable |

## Expert Judgement

**Expert expresses judgment about possible drug causation after taking into account all available & relevant data of the specific case.**

| | | |
|---|---|---|
| Subjective | Poor reproducibility | Inter- intra rater disagreement |

## Algorithms

## Naranjo's Algorithm

| Questions | Yes | No | Don't know |
|---|---|---|---|
| Presence of previous conclusive report on adverse reaction. | +1 | 0 | 0 |
| Did adverse event appear subsequent to administration of suspected drug? | +2 | -1 | 0 |
| Did adverse event improve on drug discontinuation or on administration of specific antagonist? | +1 | 0 | 0 |
| Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0 |
| Are there any alternative causes other than the suspected drug that could have caused the reaction on their own? | -1 | +2 | 0 |
| Did the adverse event reappear when a placebo was administered? | -1 | +1 | 0 |
| Was the incriminated drug detected in toxic concentrations in blood (fluids)? | +1 | 0 | 0 |
| Did the adverse event worsen on increasing the dose or decreased in severity with lower doses? | +1 | 0 | 0 |
| Past history of any similar reaction to the same or similar drugs. | +1 | 0 | 0 |
| Was the adverse event confirmed by objective evidence? | +1 | 0 | 0 |
| **Total score 0– Doubtful 1–4 Possible, 5–8 Probable, ≥9 Definite** | | | |

## Probabilistic/ logistic methods (Bayesian approaches)

**Sets starting point (i.e. prior probability or odds)**

- background information on drug – event association (e.g.incidence of adverse event with and without treatment)

**Considers relevant information for specific case (i.e. likelihood ratio)**

- probability of positive test result among drug-caused event population & among nondrug-caused event population by transforming it into a multiplying factor

## Probabilistic/ logistic methods (Bayesian approaches)

**Obtains precise estimate of drug causation on a continuous scale**

- ranging from 0 to 1 for probability/ from 0 to infinity for odds

**Follows the basic rule of probability theory**

- ie in the absence of relevant information, obtains neutral estimate (i.e., a probability of .5 or an odds of 1)

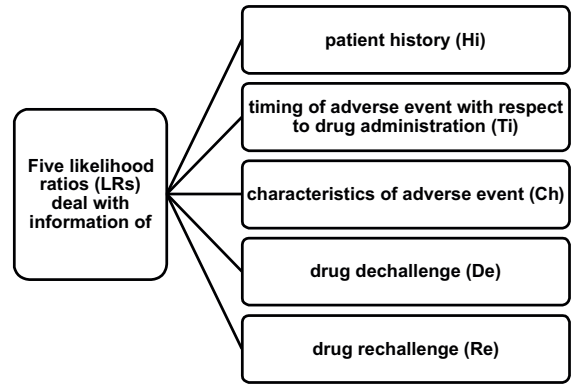
## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

- Developed to overcome limitations associated with expert judgements & algorithms
- Calculates posterior odds in favour of particular drug causing ADR as compared to alternative causes
- Posterior odds factor is calculated using 6 assessment subsets:
  - one deals with background information (prior odds)
  - five deals with case specific information (likelihood ratios).

## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

- Prior odds (PrO):
  - Odds before the test
  - ratio of expected drug-attributable risk & background risk of certain adverse event in a population sharing basic characteristics with patient being considered

## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)




## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

**Posterior odds (PsO):**

**product of prior ODDs & likelihood ratios**

PsO = PrO - LR(Hi) - LR(Ti) - LR(Ch) - LR(De) - LR(Re)

## Probabilistic/ logistic methods (Bayesian approaches)

**Prior probability calculated from epidemiological information and clinical trial**

**Posterior probability combines this background information with evidence in individual case**

**open-ended without limit for details to be assessed**

**Provides scope for simultaneous assessment of multiple causes**

## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

- Calculates posterior probability in favor of a specific drug compared to other drug or nondrug etiologies of an adverse event based on
  - background (eg, epidemiologic) and
  - case information (eg, time of onset).
- discriminates between multiple drug and nondrug etiologies.

## Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

| | | |
|---|---|---|
| can be implemented as spreadsheet programme | provides feedback following new evidence of ADR | Apt descriptions from literature are listed to assess prior probability |
| considers elements to distinguish potential causes | evaluates more than 2 possible causes at the same time | allows for rapid calculation & interaction during the process |

| | |
|---|---|
| requires expertise to operate | widespread use is limited by complexity & time required |

## MacBARDI spreadsheet

- Based on BARDI built in spreadsheet on Apple Macintosh SE microcomputer for assessing drug induced neutropenia
- used for assessing
  - pulmonary fibrosis with antiarrhythmics
  - cutaneous reactions with sulfonamides & anticonvulsants
  - fetal alcohol syndrome
  - benzodiazepine withdrawal.

## MacBARDI spreadsheet

Requires five information:

- information lines for the input needed
- input lines for the parameters used to calculate each of the six factors
- assumption lines for in-built inputs
- calculation lines that calculate & show the value of each term in the assessment
- output lines, to show value of each factor necessary to calculate posterior odds

## MacBARDI spreadsheet

- updates analyses as new information becomes available
- encourages learning & modelling
- decreases time required to assess cases
- does not have automatic database lookup
- assessor has to find relevant information on database and enter on spreadsheet.

## MacBARDI spreadsheet

| Merits | Limitations |
|---|---|
| • **Reliability** | • **Time** |
| • **Explicitness** | • **Resources** |
| • **Transparency** | • **Complex designs** |

## Logistic methods

- probability for drug causation using logistic function, (statistically weighted by consensual expert judgement)
- In the absence of any argument in favour /disfavour of drug responsibility, sum of weights is equal to 0 and probability of drug causation fixed at 0.5.
- If arguments in disfavour of drug responsibility, sum of weights inferior to 0 and the probability less than 0.5
- If arguments in disfavour of drug responsibility, sum of weights inferior to 0 and the probability less than 0.5

## Logistic method

Arimone et al (2006) proposed new approach based on

- logistic function to model expert judgment
- scientific weighting using a statistical approach

Provides range of causation probability from .01 to .99

## Logistic method

**7 assessment criteria**

- time of onset
- dechallenge
- rechallenge
- search for non drug-related causes
- risk factor(s)
- reaction at site or validated laboratory test in favor of drug's responsibility
- previous reports or publication of similar event, and/or symptoms suggestive of a drug causation

Crude results obtained from the multilinear regression on logit($p$) and rounded weighting for the final model

| Criteria | Statistical weights | 95% CI | Final weight |
|---|---|---|---|
| Time to onset | | | |
| Incompatible | −3.95 | −5.93; −1.97 | (−4) STOP |
| Not suggestive | −1.1 | −2.77; 0.57 | −1 |
| Unknown or not available | 0 | — | 0 |
| Compatible | 0.21 | −0.64; 1.06 | 0.5 |
| Highly suggestive | 0.72 | −0.41; 1.85 | 1 |
| Dechallenge | | | |
| Against the role of the drug | — | — | −0.5 |
| Not conclusive or not available | 0 | — | 0 |
| Suggestive | 0.42 | −0.33; 1.17 | 0.5 |
| Rechallenge | | | |
| Negative | — | | −0.5 |
| Not attempted or not interpretable | 0 | — | 0 |
| Positive | 0.41 | −0.84; 1.67 | 0.5 |
| Search for non-drug-related causes | | | |
| Nondrug cause highly probable | −2.21 | −3.74; −0.69 | −2 |
| Not investigated and/or possible nondrug cause | 0 | — | 0 |
| Nondrug causes ruled out | 0.86 | −0.01; 1.72 | 1 |
| Risk factors for drug reaction | | | |
| Ruled out or absent | 0 | — | 0 |
| Well validated and present | 0.53 | −0.19; 1.26 | 0.5 |
| Reaction at site of application, or relevant and reliable laboratory test strongly in favor of the drug responsibility | | | |
| Unrelated or not available | 0 | — | 0 |
| Present and/or positive | 0.38 | −0.57; 1.32 | 0.5 |
| Previous reports of similar drug–event associations and symptoms evocative of a drug causation | | | |
| Reaction not previously reported and type B reaction[a] | −0.38 | −1.75; 0.98 | −0.5 |
| Not available | 0 | — | 0 |
| Labeled reaction and/or type A reaction[a] | 0.24 | −0.6; 1.08 | 0.5 |

[a] Reaction type according to Rawlins and Thompson, 1977 [22].

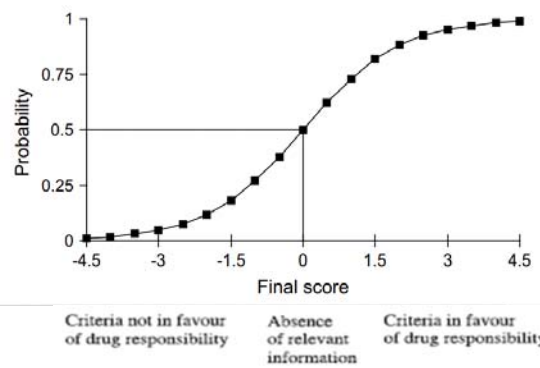
## Logistic methods

Probabilities of drug causation corresponding to sum of scores (by logistic transform)[a]

| Final score, sum of weights | Corresponding probability, % |
|---|---|
| −4.5 | 1 |
| −4 | 2 |
| −3.5 | 3 |
| −3 | 5 |
| −2.5 | 8 |
| −2 | 12 |
| −1.5 | 18 |
| −1 | 27 |
| −0.5 | 38 |
| 0 | 50 |
| 0.5 | 62 |
| 1 | 73 |
| 1.5 | 82 |
| 2 | 88 |
| 2.5 | 92 |
| 3 | 95 |
| 3.5 | 97 |
| 4 | 98 |
| 4.5 | 99 |

[a] Probability of drug causation $p = 1/[1 + \exp(-\text{final score})]$.

## Logistic method



## Case reference report

- 68-year-old man had a medical history of chronic lymphoid leukemia, allergy to amoxicillin, and hematuria attributed to aspirin 15 years ago. He was hospitalized from April 6 to 14 for acute myocardial infarction and treated with aspirin 250 mg/day, ramipril, furosemide, potassium chloride, and ropinirole. On April 18, he reported a melena but said that the symptoms occurred when the therapy was begun. The etiologic search confirmed anemia (hemoglobin 8.3 g/dL) and a duodenal ulcer.

- The issue is to determine if the occurrence of the melena is related to the aspirin.

## Case reference report

**Time to onset**

- Aspirin was started on the day of the event but prior to its occurrence. Therefore, the time to onset is considered compatible (score: 0.5).

**Rechallenge and Dechallenge**

- rechallenge & dechallenge criteria not relevant

- considered ‘‘not conclusive or not available’’ (score: 0 for each criterion).

## Case reference report

**Search for non-drug-related causes**

- Assessing search for non-drug-related causes consists of reviewing main possible nondrug causes of adverse event. Another alternative could have been a gastric carcinoma; this was ruled out by endoscopy which showed presence of duodenal ulcer. There is no reasonable alternative nondrug-related explanation for this adverse event. This criterion is quoted as ‘‘nondrug causes ruled out’’ (score: 1).

## Case reference report

**Risk factors for drug reaction**

- occurrence of hematuria with aspirin 15 years ago and the age of this patient (68 years) are well-validated risk factors for melena with same medication. This criterion is considered ‘‘well validated and present’’ (score: 0.5).

**Reaction at site of application or relevant and reliable laboratory test strongly in favor of drug responsibility.**

- neither reaction at site of application nor validated laboratory test in favor of responsibility for the drug (score: 0).

## Case reference report

**Previous reports of similar drug–event associations and symptoms evocative of a drug causation**.

- Melena is an expected effect of aspirin; considered ‘‘labeled reaction and/or type A reaction’’ (score: 0.5).

**Transform to final probability.**

- Sum of weighting scores is 2.5. Transformation of this value by the logistic formula leads to a probability of .92.

## Logistic method

Drug Saf. 2010 Nov 1;33(11):1045-54. doi: 10.2165/11537780-000000000-00000.

**Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre.**

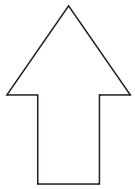
Théophile H[1], Arimone Y, Miremont-Salamé G, Moore N, Fournier-Réglat A, Haramburu F, Bégaud B

**Table VII.** Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the logistic method and the French algorithm taking experts' consensus as reference, where neutral consensual expert judgements, i.e. p=0.45–0.55, were considered as possibly in favour of drug responsibility

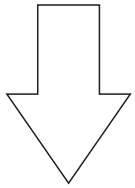
| Parameter | Logistic method | French algorithm |
|---|---|---|
| Sensitivity | 0.95 | 0.32 |
| Specificity | 0.42 | 0.92 |
| PPV | 0.84 | 0.92 |
| NPV | 0.71 | 0.30 |

**CONCLUSIONS:** Agreement between the three approaches was poor, and only satisfactory for drug events judged as drug-induced by consensual expert judgement. The logistic method showed high sensitivity at the expense of poor specificity. Conversely, the algorithm had poor sensitivity but good specificity. The comparatively good sensitivity and positive predictive values of the logistic method suggest that it may be more useful in the routine or automated assessment of case reports of suspected but still unknown adverse drug reactions. With a substantial rate of false positives relative to true negatives (low specificity), the logistic method does not replace, but can be complemented by, critical clinical assessment of individual cases in evaluating drug-related risk.

## Logistic method



statistically weighted with reference to expert judgement



Poor specificity

Overestimation of probability of drug causation.

## New version of Logistic method

- weighs different options offered by each criterion with statistical approach based on a consensus of two groups of senior experts as reference
- probability for drug causation is decreased in the absence of investigations to rule out alternative causes for the event
- discriminant value is improved because all probability values from 0 to 1 can now be produced.
- assessment process is fast & more appropriate

Theophile et al, 2012

| New version of logistic method | Statistical weights |
|---|---|
| 1) Time to onset | |
| Incompatible | - 5 |
| Not suggestive | - 0.48647 |
| Unknown or not available | 0 |
| Compatible | + 0.72218 |
| Highly suggestive | + 0.79190 |
| 2) Dechallenge | |
| Against the role of the drug | - 1.32394 |
| Non-conclusive or not available | 0 |
| Suggestive | + 0.45961 |
| 3) Rechallenge | |
| Negative | - 0.97045 |
| Not attempted or not conclusive | 0 |
| Positive | + 0.1911 |
| 4) Search for other aetiology | |
| Another cause highly probable | - 2.74122 |
| Required and not investigated or/and another possible cause | - 1.04487 |
| Not required and/or not applicable | 0 |
| Another cause ruled out | +0.16723 |
| 5) Risk factor(s) for drug reaction | |
| Ruled out or absent | 0 |
| Well validated and present | + 1.18048 |
| 6) Reaction at site of application or plasma concentration known as toxic or validated laboratory test | |
| Unrelated or not available | 0 |
| Present or/and positive | + 1.25352 |
| 7) Previous information on the drug and symptomatology | |
| Reaction not previously reported and type B | - 0.42331 |
| Not available0 | 0 |
| Not well known or previously published once or twice | + 0.02686 |
| Well known and labelled reaction | + 0.36131 |

## New version of Logistic method

**Table 4.** Sensitivity, specificity, PPV, and NPV of the initial and new versions of the logistic method taking expert consensus as reference on a randomly sample of 59 drug-event pairs

| Parameter | Initial version of the logistic method | New version of the logistic method |
|---|---|---|
| Sensitivity | 1 | 0.96 |
| Specificity | 0.33 | 0.56 |
| PPV | 0.89 | 0.92 |
| NPV | 1 | 0.71 |

*Abbreviations:* PPV, positive predictive value; NPV, negative predictive value.

## New version of Logistic method

Drug Saf. 2013 Oct;36(10):1033-44. doi: 10.1007/s40264-013-0083-1.

**Comparison of three methods (an updated logistic probabilistic method, the Naranjo and Liverpool algorithms) for the evaluation of routine pharmacovigilance case reports using consensual expert judgement as reference.**

Théophile H[1], André M, Miremont-Salamé G, Arimone Y, Bégaud B

Author information

**Abstract**

**BACKGROUND:** An updated probabilistic causality assessment method and the Liverpool algorithm presented as an improved version of the Naranjo algorithm, one of the most used and accepted causality assessment methods, have recently been proposed.

**OBJECTIVE:** In order to test the validity of the probabilistic method in routine pharmacovigilance, results provided by the Naranjo and Liverpool algorithms, as well as the updated probabilistic method, were each compared with a consensual expert judgement taken as reference.

**METHODS:** A sample of 59 drug-event pairs randomly sampled from spontaneous reports to the French pharmacovigilance system was assessed by expert judgement until reaching consensus and by members of a pharmacovigilance unit using the updated probabilistic method, the Naranjo and Liverpool algorithms. Probabilities given by the probabilistic method, and categories obtained by both the Naranjo and the Liverpool algorithms were compared as well as their sensitivity, specificity, positive and negative predictive values.

**RESULTS:** The median probability for drug causation given by the consensual expert judgement was 0.70 (inter-quartile range, IQR 0.54-0.84) versus 0.77 (IQR 0.54-0.91) for the probabilistic method. For the Naranjo algorithm, the 'possible' causality category was predominant (61 %), followed by 'probable' (35 %), 'doubtful', and 'almost certain' categories (2 % each). Category distribution obtained with the Liverpool algorithm was similar to that obtained by the Naranjo algorithm with a majority of 'possible' (61 %) and 'probable' (30 %) followed by 'definite' (7 %) and 'unlikely' (2 %). For the probabilistic method, sensitivity, specificity, positive and negative predictive values were 0.96, 0.56, 0.92 and 0.71, respectively. For the Naranjo algorithm, depending on whether the 'possible' category was considered in favour or in disfavour of drug causation, sensitivity was, respectively, 1 or 0.42, specificity 0.11 or 0.89, negative predictive value 1 or 0.22 and positive predictive value 0.86 or 0.95; results were identical for the Liverpool algorithm.

**CONCLUSION:** The logistic probabilistic method gave results closer to the consensual expert judgment than either the Naranjo or Liverpool algorithms whose performance were strongly dependent on the meaning given to the 'possible' category. Owing to its good sensitivity and positive predictive value and by providing results as continuous probabilities, the probabilistic method seems worthy to use for a trustable assessment of adverse drug reactions in routine practice.

## New version of Logistic method

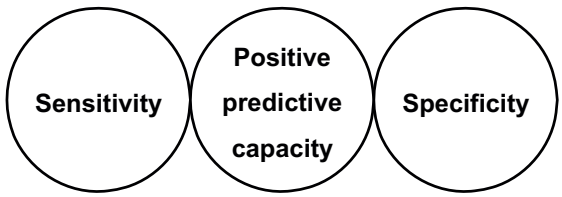
**Table 3** Causality assessments given by the four approaches for the 59 drug–event pairs

| Case no. | Expert probability | Logistic method probability | Naranjo category | Liverpool category | Case no. | Expert probability | Logistic method probability | Naranjo category | Liverpool category |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.01 | 0 | Doubtful | Unlikely | 31 | 0.7 | 0.84 | Possible | Possible |
| 2 | 0.15 | 0.23 | Possible | Possible | 32 | 0.72 | 0.83 | Probable | Probable |
| 3 | 0.18 | 0.32 | Possible | Possible | 33 | 0.75 | 0.62 | Possible | Possible |
| 4 | 0.25 | 0.43 | Possible | Possible | 34 | 0.75 | 0.62 | Possible | Possible |
| 5 | 0.30 | 0.78 | Probable | Probable | 35 | 0.75 | 0.77 | Possible | Possible |
| 6 | 0.47 | 0.43 | Possible | Possible | 36 | 0.77 | 0.84 | Possible | Possible |
| 7 | 0.47 | 0.62 | Possible | Possible | 37 | 0.78 | 0.62 | Possible | Possible |
| 8 | 0.48 | 0.51 | Possible | Possible | 38 | 0.78 | 0.85 | Probable | Probable |
| 9 | 0.48 | 0.51 | Possible | Possible | 39 | 0.80 | 0.77 | Possible | Possible |
| 10 | 0.5 | 0.51 | Possible | Possible | 40 | 0.8 | 0.85 | Possible | Possible |
| 11 | 0.5 | 0.51 | Possible | Possible | 41 | 0.81 | 0.84 | Possible | Possible |
| 12 | 0.51 | 0.43 | Possible | Possible | 42 | 0.81 | 0.98 | Probable | Probable |
| 13 | 0.51 | 0.78 | Probable | Definite | 43 | 0.83 | 0.62 | Possible | Possible |
| 14 | 0.53 | 0.85 | Probable | Probable | 44 | 0.84 | 0.91 | Probable | Probable |
| 15 | 0.54 | 0.51 | Possible | Possible | 45 | 0.84 | 0.94 | Probable | Probable |
| 16 | 0.55 | 0.82 | Possible | Possible | 46 | 0.86 | 0.62 | Possible | Possible |
| 17 | 0.55 | 0.94 | Probable | Probable | 47 | 0.87 | 0.94 | Probable | Probable |
| 18 | 0.57 | 0.54 | Possible | Possible | 48 | 0.88 | 0.94 | Probable | Probable |
| 19 | 0.58 | 0.54 | Possible | Possible | 49 | 0.88 | 0.94 | Probable | Probable |
| 20 | 0.61 | 0.54 | Possible | Possible | 50 | 0.92 | 0.95 | Probable | Probable |
| 21 | 0.61 | 0.64 | Possible | Possible | 51 | 0.93 | 0.83 | Probable | Probable |
| 22 | 0.63 | 0.62 | Possible | Possible | 52 | 0.93 | 0.94 | Probable | Probable |
| 23 | 0.63 | 0.64 | Possible | Possible | 53 | 0.93 | 0.96 | Almost certain | Definite |
| 24 | 0.63 | 0.82 | Possible | Possible | 54 | 0.94 | 0.94 | Probable | Probable |
| 25 | 0.65 | 0.51 | Possible | Possible | 55 | 0.95 | 0.48 | Possible | Possible |
| 26 | 0.67 | 0.75 | Possible | Possible | 56 | 0.95 | 0.98 | Probable | Definite |
| 27 | 0.68 | 0.77 | Possible | Possible | 57 | 0.96 | 0.95 | Probable | Probable |
| 28 | 0.69 | 0.54 | Possible | Possible | 58 | 0.97 | 0.95 | Probable | Probable |
| 29 | 0.69 | 0.62 | Possible | Possible | 59 | 0.98 | 0.98 | Probable | Definite |
| 30 | 0.70 | 0.91 | Probable | Probable | | | | | |

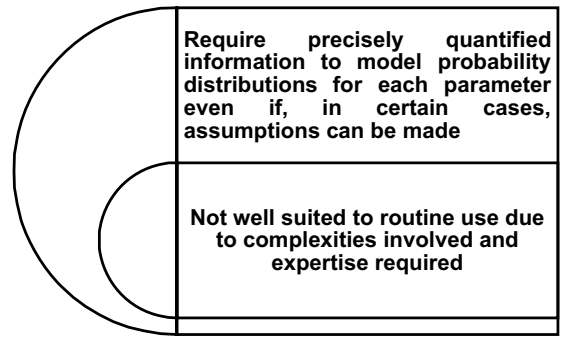
## New version of Logistic method

**Table 5** Sensitivity, specificity, positive predictive value (*PPV*), negative predictive value (*NPV*) and accuracy of the updated logistic, the Naranjo and Liverpool methods, taking experts consensus as reference

| | Logistic method | Naranjo method 1 | Naranjo method 2 | Liverpool method 1 | Liverpool method 2 |
|---|---|---|---|---|---|
| Sensitivity | 0.96 | 1 | 0.42 | 1 | 0.42 |
| Specificity | 0.56 | 0.11 | 0.89 | 0.11 | 0.89 |
| PPV | 0.92 | 0.86 | 0.95 | 0.86 | 0.95 |
| NPV | 0.71 | 1 | 0.22 | 1 | 0.22 |
| Accuracy | 0.90 | 0.86 | 0.49 | 0.86 | 0.49 |




## Probabilistic/ logistic methods (Bayesian approaches)




## Expert Judgement

| | |
|---|---|
| Certain | • Event or laboratory test abnormality, with plausible time relationship to drug intake<br>• Cannot be explained by disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon)<br>• Rechallenge satisfactory, if necessary |
| Probable/ likely | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not required |
| Possible | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Could also be explained by disease or other drugs<br>• 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)<br>• Disease or other drugs provide plausible explanation |
| Conditional/ unclassified | • Event or laboratory test abnormality<br>• More data for proper assessment needed, or<br>• Additional data under examination |
| Unassessable/ unclassifiable | • Report suggesting an adverse reaction<br>• Cannot be judged because information is insufficient or contradictory<br>• Data cannot be supplemented or verified |

## Algorithms

| Questions | Yes | No | Don't know |
|---|---|---|---|
| Presence of previous conclusive report on adverse reaction. | +1 | 0 | 0 |
| Did adverse event appear subsequent to administration of suspected drug? | +2 | -1 | 0 |
| Did adverse event improve on drug discontinuation or on administration of specific antagonist? | +1 | 0 | 0 |
| Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0 |
| Are there any alternative causes other than the suspected drug that could have caused the reaction on their own? | -1 | +2 | 0 |
| Did the adverse event reappear when a placebo was administered? | -1 | +1 | 0 |
| Was the incriminated drug detected in toxic concentrations in blood (fluids)? | +1 | 0 | 0 |
| Did the adverse event worsen on increasing the dose or decreased in severity with lower doses? | +1 | 0 | 0 |
| Past history of any similar reaction to the same or similar drugs. | +1 | 0 | 0 |
| Was the adverse event confirmed by objective evidence? | +1 | 0 | 0 |
| **Total score 0– Doubtful 1–4 Possible, 5–8 Probable, ≥9 Definite** | | | |

| New version of logistic method | Statistical weights |
|---|---|
| 1) Time to onset | |
| Incompatible | - 5 |
| Not suggestive | - 0.48647 |
| Unknown or not available | 0 |
| Compatible | + 0.72218 |
| Highly suggestive | + 0.79190 |
| 2) Dechallenge | |
| Against the role of the drug | - 1.32394 |
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| 3) Rechallenge | |
| Negative | - 0.97045 |
| Not attempted or not conclusive | 0 |
| Positive | + 0.1911 |
| 4) Search for other aetiology | |
| Another cause highly probable | - 2.74122 |
| Required and not investigated or/and another possible cause | - 1.04487 |
| Not required and/or not applicable | 0 |
| Another cause ruled out | +0.16723 |
| 5) Risk factor(s) for drug reaction | |
| Ruled out or absent | 0 |
| Well validated and present | + 1.18048 |
| 6) Reaction at site of application or plasma concentration known as toxic or validated laboratory test | |
| Unrelated or not available | 0 |
| Present or/and positive | + 1.25352 |
| 7) Previous information on the drug and symptomatology | |
| Reaction not previously reported and type B | - 0.42331 |
| Not available0 | 0 |
| Not well known or previously published once or twice | + 0.02686 |
| Well known and labelled reaction | + 0.36131 |

## Which is the best METHOD for CAUSALITY ASSESSMENT ???

Due to lack of reproducibility & validity, no single method is universally accepted.

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# ROLE OF HEALTHCARE PROFESSIONALS INCLUDING PHARMACISTS IN PHARMACOVIGILANCE

by

**Dr. Guru Prasad Mohanta,**
**Professor of Pharmacy, (Former National Technical Officer,**
**WHO Country Office for India), Annamalai University, Annamalai Nagar**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Medicines are Different from Other Commodities

"The one who pays does not decide and one who decides does not pay"

"The one who decides is often paid"

### Quotes

- I do not want two diseases: one nature made and one doctor made.

  Napoleon Bonaparte

- I firmly believe that if the whole of the material medica, as now used, could be sunkto the bottom of the sea, it would be all better for mankind and the all the worse forthe fishes.

  Oliver Wendell Holmes, 1860

## Monitoring ADRs ---

- Not just restricted to reporting of safety aspects.
- ADRs have the potential to provide insights into Structure – Activity Relationship; Pharmacodynamics; Pharmacokinetics; Genetic Factors.
- May lead to other novel indications.

## Concerned Parties in Pharmacovigilance

- Drug Regulatory Authority
- Pharmaceutical companies
- Healthcare Professionals
- WHO and UMC
- National Centre
- Academia
- Media and Consumer Organizations

## Who are Health Professionals?

They maintain health in humans through the Application of Principles and Procedures of Evidence Based Medicines.

- Medical Doctors
- Nursing Professionals
- Midwifery Professionals
- Dentists
- Pharmacists

### Are we recognized as Health Professionals?

- 2002 Health Policy
- Pharmacists' Day
- 2017 Health Policy

## FIP Statement of Policy
## The Role of the Pharmacist in Pharmacobigilance

- PV is a clinical discipline and it serves as an indicator of standards of clinical care practiced.
- Healthcare system with PV in the system:
  - Ensure safety by minimizing the occurrence of ADR to medicines and reduce fatalities resulting from them.
  - Provide warning network among the various healthcare providers, regulators, manufacturers and consumers so that remedial action can be exercised in a timely and orderly manner.

## FIP Statement - Responsibilities

- Early detection of ADRs and other drug related issues.
- Monitoring the effectiveness of medicines.
- Source of information and critical evaluation of drug information – the degree to which the clinicians are informed of principles of PV and practice according to them will have alrge impact on quality.
- In addition to identifying the early detection of ADR, they would be able to identify the special groups with exceptional sensitivity.

## A Report on
## Challenges & Opportunities
## for Pharmacist in Health Care in India

Pharmacists need to be actively involved in the surveillance of drug safety issues within the context of their practices. Greater participation by pharmacists in all practices settings would be an important tool to increase the reporting of ADRs and other drug-related problems in pharmacovigiance.

Pharmacy educators should ensure that the curriculum is so amended that the importance of pharmacist in pharmacovigilance gets properly highlighted.

## Community Pharmacy

To begin with:

- Maintain ADR forms, report any ADRs related by patients to the centre as applicable under the National and other Pharmacovigilance programmes.

To progress with

- Take up ADRs reporting as a professional responsibility
- Enroll with reporting centres, publicize and report ADRs
- Be alert to identify potential case / screening of ADRs

## Hospital Pharmacy

To begin with

- Identifying, reporting ADRs
- Awareness about the system

To progress with

- Pharmacists play a proactive role in having ADR detection, reporting, and monitoring system in place in the hospital. The pharmacist maintains all the records, as well as disseminates information received from the reports to the healthcare team

## Clinical Pharmacy

Physicians in our country are always busy, and cannot of ten afford much time for a patient. Sometimes a patient needs to get an appointment to report a complaint after taking a medicine. Generally a patient chooses not to report the same, to avoid a cumbersome process of seeking an appointment. In some cases, physicians also avoid ADR reporting in anticipation that patients may get scared. Pharmacists being the most easily accessible health care professionals, can serve an important role in ADR monitoring programme, by acting as a link between the patient and the doctor / the regulatory authorities.

•

## Hospital Based Approach

- Reporting an ADR
- Investigation and Analysis
- Discussion and Evaluation of report
- Reporting to National Centre / Manufacturer / Regulating Authorityance gets properly highlighted.

## National Health Programmes

- TB, HIV Programme

Pharmacists need to be actively involved in the surveillance of drug safety issues within the context of their practices. Greater participation by pharmacists in all practice setting would be an important tool to increase the reporting of ADRs and other drug-related problems in pharmacovigilance.

## Competence

Dr. Marie Lindquist, Director of Uppsala Monitoring Centre, compares the Pharmacovigilance activities with observational skills of the Sherlock Homes. With his attention to every detail and its meaning and implication help Sherlock to analyze the situation in logical way and solve the mystery. She quotes Sherlock **"when you have eliminated the impossible, whatever remains, however improbable, must be the truth".**

## Competency

- They are more likely to identify and report important ADRs, if they have confidence:
  - Ability to diagnose, manage and prevent such reactions;
  - Enhanced awareness of balance between the benefits and harms of the medicines;
  - Quality information is accessible.

## KAP – Pharmacists [Perspectives in Clinical Research]

| Qualification | Number [Percent] |
|---|---|
| D. Pharm. | 40 [10] |
| B. Pharm. | 80 [20] |
| M. Pharm. | 125 [31] |
| PhD | 45 [11.5] |
| PharmD | 100 [27.5] |

## Knowledge

**Table 2: Knowledge of ADR reporting and monitoring by pharmacists**

| Questions | Response | | |
|---|---|---|---|
| | Yes *n* (%) | No *n* (%) | Not sure *n* (%) |
| Do you know what are ADRs? | 381 (95) | 9 (2.5) | 10 (2.5) |
| Are you aware about the national pharmacovigilance program? | 230 (57.5) | 110 (27.5) | 60 (15) |
| Do you know the nearest pharmacovigilance center located from your working place? | 120 (30) | 220 (55) | 60 (15) |
| Do you believe all drugs available in the market are safe? | 20 (5) | 360 (90) | 20 (5) |
| Do you believe herbal products have no ADRs, i.e. they are safe? | 64 (16) | 296 (74) | 40 (10) |
| ADRs associated with herbal products should not be reported | 25 (6) | 295 (74) | 80 (20) |

## Attitudes

**Table 3: Responses of professionals to the attitude related questions**

| Questions | Response | | |
|---|---|---|---|
| | Yes | No | Not sure |
| Do you think reporting ADR is a pharmacist's duty? | 325 (81) | 40 (10) | 35 (9) |
| Do you think serious ADRs encourage pharmacists to report it to the relevant authority? | 340 (85) | 40 (10) | 20 (5) |
| Do you believe ADR reporting should be made mandatory for practicing pharmacists? | 360 (90) | 24 (6) | 16 (4) |
| ADR reporting in India is not widely promoted by relevant authorities | 320 (80) | 20 (5) | 60 (15) |
| Are you interested in participating in the ADR reporting system? | 350 (87.5) | 20 (5) | 30 (7.5) |
| What is your expectation from the pharmacovigilance program? | Responses *n* (%) | | |
| Someone from the local pharmacovigilance center to coordinate with you | 300 (75) | | |
| Financial compensation for time and energy spent | 100 (25) | | |

## Practice

**Table 4: ADR reporting in your workplace (practice)**

| Questions | Response | | |
|---|---|---|---|
| | Yes | No | Not sure |
| Did you observe any ADR cases in your practice? | 190 (47.5) | 170 (42.5) | 40 (10) |
| If yes, then to whom have you reported | Responses *n* (%) | | |
| HOD of your institute | | 50 (26) | |
| Drug manufacturer | | 27 (14) | |
| Government of India | | 3 (1.5) | |
| CDSCO | | 70 (37) | |
| Other | | 40 (21) | |
| Is ADR reporting form available at your workplace? | 100 (25) | 250 (62.5) | 50 (12.5) |
| Does your workplace provide information regarding the procedure of reporting ADRs? | 150 (37.5) | 200 (50) | 50 (12.5) |
| Do you feel that you are adequately trained in ADR reporting? | 120 (30) | 230 (57.5) | 50 (12.5) |
| Does your workplace encourage you to report an ADR? | 120 (30) | 180 (45) | 100 (25) |

## Take Home Message

"No medicine is 100% safe for all people in all circumstances"

"It is understandable that the patients die of lack of access to medicines.

But, it is not acceptable that the patients die of medicines."

This is a noble and satisfying area to work in Pharmacovigilance. Let's ensure the medicines available for us as well as for our future generation Safe and Effective.

## What we can do as Health Professionals?

- Detect, investigate, manage and report ADRs, medication errors and quality issues;
- Counsel Patients;
- Educate trainee professionals;
- Help in establishing a PV system in health setup.

## Seven Deadly Sins [William Inman]

- The mistaken believe that only safe drugs are approved for use.
- Fear of litigation.
- A sense of guilt for having caused the harm.
- Ambition to collect and publish a personal series of cases.
- Ignorance of mechanism for reporting suspected reaction.
- Diffidence about reporting a mere suspicious.
- Lethargy or indifference to doctor's responsibility to contribute to the general advancement of knowledge.

## Minimum Data Required – For Causality Analysis

- An identifiable source of information or reporter.
- An identifiable patient.
- Name(s) of the suspected product(s).
- A description of the suspected reaction(s).

### Causality Assessment

- Is there a convincing relationship between the drug and event?
- Did the drug actually cause the event?
  - Certain (Definite).
  - Probable.
  - Possible.
  - Unlikely.
  - Unclassified (Conditional)
  - Un-assessable (Unclassifiable).

## Career Opportunities

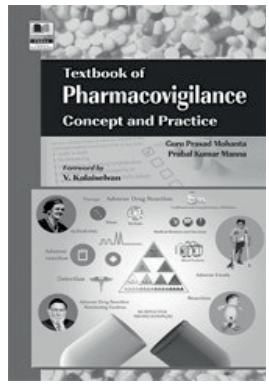
- Clinical Research – Excellent Opportunities for Building Career.
- PSUR Mandatory.
- All the Big Indian Pharma companies have Pharmacovigilance department and they hire large number.
- Software companies like TCS, Accenture, WIPRO, Cognigent, Infosys etc.
- CROs for the PV.
- Government – PV Officer in every district

## Some Free Source of Information

- Pharmaceutical Newsletter (www.who.int/medicines )
- Pharmacovigilance Toolkit: http://pvtoolkit.org/
- Australian Prescriber (www.australianprescriber.com )
- Uppsala Reports ( www.who-umc.org)


## Ultimate Goals of Pharmacovigilance

- The rational and safe use of medical drugs
- The assessment and communication of the risks and benefits of drugs on the market
- Education and informing of patients




# INTEGRATING NATIONAL HEALTH PROGRAMS WITH PvPI

by

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**Regional Pharmacovigilance Centre, Kilpauk Medical College, Chennai**

(Lecture delivered during Pharmacovigilance Training Course conducted by Trust - 3rd to 5th August 2017)

## Utilizing the hospitals

- Creating surveillance centres
- Recruiting willing Doctors
- Training for medical and paramedical staff
- ADR Recording for every patient
- Daily reports

- Readymade, laptop-based data entry
- Sample size – based actions
- Intensive monitoring for some selected drugs
- Follow-up interviews
- Involving medical personnel

## Advantages

- Looking into numerator and denominator
- Risk/benefit analysis
- Sharing info with clinicians
- Splitting the work among different centres

## Main issue

- Doubts about reporter's identity and institution's identity

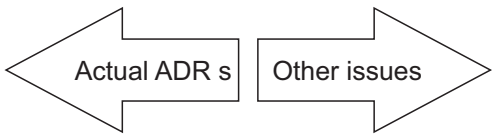
## Previous studies done and findings

- Long term use and follow up (Dr Kalaiselvan et al)
- Regular interactive sessions
- ability to produce rates, rapid results, and early detection of signals, fewer missing data and less reporting bias
- active pharmacovigilance surveillance/CEM for newly launched FDCs

## Specific issues

- Drug standards
- Storage standards
- Medication errors
- Vaccine reactions
- New vaccines being introduced
- No spontaneous reporting culture

### Differentiate




## Some strategies

- Cohort event monitoring
- Targeted spontaneous monitoring
- Patient-centred education materials/audio visual aids

### Programmes for Communicable Diseases

- National Vector Borne Diseases Control Programme (NVBDCP)
- Revised National Tuberculosis Control Programme
- National Leprosy Eradication Programme
- National AIDS Control Programme
- Universal Immunization Programme
- Integrated Disease Surveillance Programme

### Programmes for Non Communicable Diseases

- National Cancer Control Program
- National Mental Health Program
- National Diabetes Control Program
- National Program for Control and treatment of Occupational Diseases
- National Program for Control of Blindness
- National program for control of diabetes, cardiovascular disease and stroke
- National program for prevention and control of deafness

### National Nutritional Programs

- Integrated Child Development Services Scheme
- Midday Meal Programme
- Special Nutrition Programme (SNP)
- National Nutritional Anemia Prophylaxis Programme
- National Iodine Deficiency Disorders Control Programme

### Programs related to System Strengthening /Welfare

- National Rural Health Mission
- Reproductive and Child Health Programme
- National Water supply & Sanitation Programme
- 20 Points Programme

### Benefits of integrating

- unknown cases are reduced
- More favorable outcomes of ADRs
- Good reporting rate

### Uniqueness of some programs

- No patients involved-Healthy people only involved-No typical Dr-patient relationship
- Increasing responsibility in relation to r/b ratio
- Causality assessment may be difficult
- Medical personnel may be absent

### Risks in programs

- Parental consent ?
- Parental presence ?
- Mass distribution of drugs
- Coincidental events

### Recommended

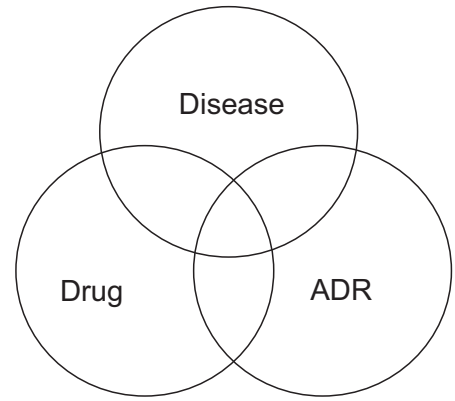
- Good pharmacovigilance practice
- Coordination
- Signal assessment committees
- Death audits in programs
- Follow-up of pregnancies

### Steps preferred

- Training
- Capacity building
- Possibility of drug interactions is an important clinically relevant area
- Use of technology
- Fast collection and analysis of data

### Often missed

- Some diseases may cause more ADRs to drugs – to be closely monitored



# EDUCATE NEXT GENERATION PHARMACIST AND PATIENTS

by
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Note: This article was awarded 3rd Prize in the Essay Competition conducted by our Trust

## Introduction

Pharmacy like every other health care professional is changing rapidly. Almost every aspect of its knowledge and practice base is affected by external change-technological developments, changing patient expectation, new professional governance's requirements, and developments in other professions. The Pharmacy education in our country has tremendous expansion in last one decade. Now we have today over 600 pharmacy colleges with annual intake of over 60,000 students at Diploma, Bachelor and Master level. However, the standard in Pharmacy education has been eroded by rising tides of mediocrity. There is a growing concern about the future of pharmaceutical education in India and it being affected by sweeping changes in the global economy. Moreover qualities of Pharmacy education imparted by our institution have everlasting impart on quality of health care offered to our society. There is an urgent need to initiate an academic exercise aimed at attaining revamping of curriculum, keeping in pace with current and emerging trends in the field of pharmacy. Any delay on our part in meeting present and future requirements of Pharmacy curriculum will be actually felt by the coming generations of our students. On the continuation of our work for the progress of Pharmacy profession, in the present work various suggestions have been made supported by student's survey in the form of simple questionnaire. This study explored the experiences and expectations of B. Pharmacy students of pharmacy education as a prelude for designing revised and advanced Pharmacy education.ting leadership skills in the pharmaceutical industry and hospital-based pharmacists.

## Suggestions

Regarding this some of the solutions and suggestions such as modification of syllabus, computer aided Pharmacy education and digital technological teaching methods should be implemented digital technologies and other methods such as video lectures and teleconferences can be used. AICTE/PCI should work in the establishment of separate pharmaceutical universities in views of proper planning and co-ordinate development of the Pharmacy education system. An interaction between

industry - academic institution is a matter of great relevance in the present context of globalization of pharmaceutical education. Six months industrial training and three months hospital training must be mandatory for all the students at the degree level. Regular revisions of practical curriculum keep space with the emerging trends in the Pharmacy field. Notable elements of quality education are the quality of students being admitted, qualification of the teachers, quality of the teachers, quality of teaching, laboratory training, examination pattern and research activities. That will enhance by all India Entrance examination for Pharmacy and conduction of seminar, refresher course, workshops etc for teachers.

**GIVING SPECIAL STATUS TO PHARMACY COURSE**

- Establishment of separate pharmaceutical university in every state.
- All the India entrance examination for admission in Pharmacy course.

**NEED FOR CHANGE: MODIFICATION OF SYLLABUS**

- Marketing course should be included which also contains atleast one month field training.
- Teaching of cellular / molecular biology in depth that will help in growing cell lines so vital to in-vitro testing of drugs.
- Introduction of regulatory affairs and patent filing course at the graduate level.
- Deletion of certain topics like trigonometry, coordinate geometry, Laplace etc in maths as they are not much use in Pharmacy.

**IMPLEMENTATION OF COMPUTER AIDED PHARMACY EDUCATION**

- Introduction of graphical representation and mathematical calculations in biopharmaceutical complexities by computer aided programming.
- Digital technologies with computer aided learning by software like CHEMWINDOW, STAT-100, and PCCA, etc.
- Digital libraries in which software like SIGMAPLOY is used for data analysis.

**IMPLEMENTATION OF DIGITAL TECHNOLOGICAL TEACHING METHODS**

- Video lectures:- From eminent persons in the field of pharmaceutical education and in industry.
- Teleconferences:- Although not very popular in India so far but such conferences will enable students to ask questions from eminent people anywhere in the world.

**INDUSTRY – INSTITUTE INTERACTION**

- Introduction of six month training should be mandatory after sixth semester.
- Introduction experts should be associated as guest faculty so that students as well as faculty member should get exposure to industrial environments.
- Collaboration with industry should be mandatory for the colleges so that industry invest time, money, equipment and technology in Pharmacy colleges so that in return, a finished product (read student) fit for the industry will produce.

**ENHANCEMENT OF FACULTY TEACHING SKILLS**

- Organising and participating in professional development activities like seminar, refresher course and workshop.
- High level training should be organized in collaboration with industry for teachers.
- Encouragement should be given to pharmacy teachers to attend international conferences and visit abroad.

**TRANSFORMATION OF PRACTICAL CURRICULUM**

- Proper balance should be maintained between patient and industry oriented practical courses.
- Three month hospital training should be organised to better understand the subject of pharmacology.

**COLLABORATION WITH FOREIGN PHARMACEUTICAL INSTITUTE**

- International exchange and cooperation in pharmaceutical education should develop.
- The statutory bodies such as AICTE, PCI etc should encourage international cooperation and networking among institution.

**CONCLUSION**

As the tidal waves of change are gathering force at the foreseeable horizon and are likely to surge forward with great speed and thrust, we take note of these moments of change and prepare our boats t withstand the same. If we move with the waves we may be sailing towards an advanced future, if we do not, we are sure to get tumbled culminating in disarray & disorganisation, choice is ours. These are changes we need in pharmaceutical education to develop and strengthen the profession for this millennium .On the basis of survey and data obtained, it was concluded that these restructuring is highly essential to meet up the future requirement of pharmaceutical educations in the era of globalisation & liberalization.

# INFORMATION

## M. PHARM & PHARM D SCHOLARSHIPS 2016-17 AWARDED BY TNPSWT

Profile of 3rd Rank Projects

### *PHARMACEUTICS*

Name: Mr. Subharaj Saha
Project Title: Design & Characterization of nano- structured lipid carriers for oral bioavailability enhancement of Atozanavir through lymphatic targeting.
College: J S S College of Pharmacy, Ooty
Guide's Name: Dr. D. Nagasamy Venkatesh

### *PHARMACEUTICAL CHEMISTRY*

Name: Mr. M. Madhuraj
Project Title: Design, Synthesis, characterization & Biological Evaluation of some novel heterocyclic derivatives as anti-tubercular agents.
College: College of Pharmacy, Madras Medical College, Chennai
Guide's Name: Dr. A. Jerad Suresh

### *PHARMACEUTICAL ANALYSIS*

Name: Mr. Birendra Kumar
Project Title: Development and validation of a HPLC method for the determination of Ranolazine residues on pharmaceutical manufacturing equipment surface by swab sampling method.
College: Vinayaka Mission College of Pharmacy, Salem
Guide's Name: Dr. B. Jayakar

### *PHARMACOLOGY*

Name: Mr. A. Vijaya Ragavan
Project Title: Neuropharmacological assessment of Desmodium gangeticum in Partial sciatic nerve ligation in rat model: Role of inflammatory mediators”
College: PSG College of Pharmacy, Coimbatore
Guide's Name: Dr. M. Ramanathan

## PHARMACOLOGY

Name: Mr. D. Balaji

Project Title: Screening of Eye Irritancy using Canavalia ensiformis (Jack Bean) seed extract – An Alternative approach for animal model.

College: Mother Theresa Post Graduate & Research Institute of Health Sciences, Puducherry

Guide's Name: Prof. Dr. S. Kavimani

## PHARMACOGNOSY

Name: Ms. S. Shanmuga Priya

Project Title: Formulation and Standardisation of Polyherbal Haematinic Capsules & its Pharmacological Evaluation

College: College of Pharmacy, Madras Medical College, Chennai

Guide's Name: Dr. P. Muthusamy

## PHARMACY PRACTICE

Name: Ms. Hesly Rajan

Project Title: A Retrospective study of prescription pattern and cost analysis of selected drugs used in coronary artery disease and angioplasty in cardiac patients

College: Swamy Vivekananda College of Pharmacy, Tiruchengode

Guide's Name: Dr. T. Tamilselvan

## PHARM D- PHARMACY PRACTICE

Name: Ms. Anu Joy Thomas, Ms. Anu Maria Jose, Ms. Liz Mathew, Ms. Manju Rosy Jose

Project Title: Dose Optimization of Meropenem in critically ill patients – A population pharmacokinetics

College: J S S College of Pharmacy, Ooty

Guide's Name: Dr. K.P. Arun

# NEWS

## USFDA Issues Warning Letter to Hyderabad-Based Vista Pharma

The USFDA has issued a warning letter to the manufacturer facility of the city-based Vista Pharmaceuticals Ltd, for 'significant violations' of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals.

The US Food and Drug Administration (FDA) officials had visited the facility located at APIIC Industrial Estate, at Gopalapalli in Nalgonda district in Telangana, from September 19 to 23, 2016.

"This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211," the FDA letter said.

"Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B)," it said.

The letter was issued on July 5 and addressed to Dhananjaya Alli, Managing Director of Vista Pharmaceutical Ltd.

The company officials were not available for comments.

"The violations cited in the letter are not intended as an all-inclusive list and the company is responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations," the FDA added.

"Failure to correct these violations may also result in FDA refusing admission of products manufactured at the facility into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3)," it added.

**Source:** *ET Healthworld, 13thJuly 2017*

## Telangana: Fake Pharma Firm Busted, Rs 5 Crore Goods Seized

The special operations team of Rachakonda on Thursday busted a fake pharma manufacturing unit in Chaitanyapuri and seized huge quantities of drugs.

According to the police, the owner of the unit, Ramakrishna, had the licence to distribute drugs manufactured by other companies. However, he recently started a manufacturing unit. Most of the products he manufactured were meant for pregnant women and children.

The police seized huge quantities of tablets, tonics, milk powder, protein supplements and other products used by pregnant women and children.

Mr. P. Venkateshwarlu, inspector of the special operations team, said that goods worth over Rs 5 crore have been seized. The drug control administration has been informed. Hunt is on to nab the partner, Rajender Reddy.

**Source:** *Deccan Chronicle, 13th October 2017.*

## US FDA Panel Nod For Biocon Breast Cancer Biosimilar

A US Food and Drug Administration panel unanimously recommended approval for Biocon's biosimilar breast cancer drug, sending the Indian biopharmaceutical company's shares to a record high on Friday. The recommendation takes Biocon closer to getting the FDA's marketing approval for Trastuzumab, which has a multi-billiondollar market globally. Trastuzumab, developed originally by Roche, is one of the most commonly used drugs to treat HER2-positive breast cancer. The Swiss company's drug is sold under the brand Herceptin worldwide and Herclon in India. A biosimilar is a copy of a biologic drug.

Biocon's shares rose as much as 10.19 per cent to an all-time high of Rs 404 10.19 per cent to an all-time high of Rs 404 on the Bombay Stock Exchange, before paring the gains and closing Friday's trading at Rs 399.20, still up 8.88 per cent in a market that remained little changed. The stock has gained 19 per cent this week.

Biocon has developed the biosimilar in collaboration with US drug maker Mylan. The US FDA's Oncology Drugs Advisory Committee voted 16-0 in favour of the eligible indications of the original product, the panel tweeted early Friday India time.

The next step for the two companies is to get a final approval from the US FDA to commercially launch the product. Biocon hopes for this approval by September 3, Chairperson Kiran MazumdarShaw said.

The product will be manufactured by Biocon for all markets globally and it also has a profit-sharing arrangement with Mylan for its markets. Globally, the trastuzumab market opportunity is close to $6.9 billion and in the US alone it is around $2.6 billion at the originator product price, she said.

While the development is positive for the company, some experts said it also signals the need for Biocon to strengthen its technical capabilities, especially since the French regulator had recently found quality-related lapses during a pre-approval inspection at its Bomassandra plant for three of its products.

"This is only the start of the process. There is no reason to be positive or negative at the moment," said Surajit Pal of Prabhudas Lilladher. "This process is also expected to take care of the GMP (Good Manufacturing Practice) activities currently under question," he added.

Biocon aims to address all concerns about its drug product facility over the next one quarter in an "expeditious manner" in order to seek an early re-inspection, Ma zumdar-Shaw said. She added that Biocon was awarded a GMP certification for its drug substance facility for trastuzumab and pegfilgrastim, another biologic drug used in the treatment of cancer.

Meanwhile, analysts said the 19 per cent gain in the stock this week has been excessive, given the risks related to production of this medicine.

"The current price fully captures the upsides in this stock," said Vishal Manchanda, analyst at Nirmal Bang. "There are multiple risks that investors must account for before the drug goes into production. The main one being a delay in approval due to eight observations given by the US FDA and 11 serious observations by the European regulator

recently. If the drug's production is delayed by more than a year, the first-mover advantage for the company could be gone."

Analysts said there were also other players also that are looking to capture market share in this drug and that they will be filing for approvals in the coming months for the drug, reducing the market opportunity for Biocon.

Some analysts prefer Aurobindo Pharma over Biocon because that stock could see a faster re-rating while its valuations continue to be cheap. Aurobindo Pharma is trading at 15 times its expected fiscal 2018 earnings, while Biocon is at 46.4 times.

**Source:** *The Economic Times, 15th July 2017.*

## Bad Medicine! Pfizer, Cipla, DRL, Other 63 Drug Firms Fail Quality Test

Pfizer, 'Dr Reddys Laboratories and Cipla are among 66 drug makers that have some of their products failing quality tests carred out by the country's drug regulator.

Samples tested from these companies were found to be not of standard quality during a drug survey carried out through the National Institute of Biologicals over two years, according to a Central Drugs Standard Control Organisation (CDSCO) notification posted in its website. At least five samples of drugs from these companies failed the tests during the 2014 -2016 survey, CDSCO said

According to the notification, 25 samples by Pfizer, nine each by Dr Reddy's and Alembic, seven by Cipla and six by Zydus Healthcare were found to be not of standard quality. It didn't specify the drugs that failed the tests.

A Pfizer spokesperson said the company was unable to confirm authenticity of products picked for the tests, or the evidence of the alleged deficiencies "as the due process of providing a sealed market sample was not followed".

Samples of the company's products were found to be fully compliant with all required specifications during tests at independent FDA-approved laboratories, the spokesperson said, adding that this was communicated to the regulatory authorities and no further action was recommended.

"Pfizer places the utmost importance on product quality and patient safety. All Pfizer products released in the market meet every national and international testing specification," the spokesperson said.

Other companies ET contacted for comment did not respond until press time.

The survey, conducted to check the proportion of substandard drugs in the country, had tested 47,012 samples from 1,719 manufacturing units, CDSCO said. Around 3.16% of these samples were found to be not of standard quality, while 0.02% were spurious.

India expects to bring down the proportion of its substandard drugs to 2% over the next three years to match global standards. The country's drug regulator has been engaged in risk-based inspections of over 250 manufacturing plants as part of its efforts to achieve this goal.

**Source:** *The Economics Time, 21st July 2017.*

## Medical Devices to Carry MRP on Packs From Jan 1, 2018: Govt

Medical devices will have to mandatorily carry maximum retail price (MRP) on packages from January 1, 2018, the government informed Parliament.

Minister of State for Road Transport and Highways, Shipping and Chemicals and Fertilisers Mansukh L Mandaviya said in a written reply in the Lok Sabha that the move followed amendments to the Legal Metrology (Packaged Commodities) Rules, 2011.

He said the consumer affairs, food and public distribution ministry has issued amendments making the rules "applicable to medical devices also".

"The rules make printing and labelling of MRP on the package mandatory. These rules shall be applicable from 1.1.2018," Mandaviya said.

He was responding to a query on whether any guideline was likely to be issued or has been issued by the ministry for medical devices to declare MRP.

The minister further said that under the Legal Metrology (Packaged Commodities) Rules, 2011, every package must bear the name, address, telephone number, e-mail of persons or of office that can be contacted in case of consumer complaints.

"The amended rules shall be applicable to e-commerce companies also," he said.

In March, drug price regulator NPPA had stated that the 22 medical devices which have been notified as 'drugs' must all carry MRP on packs.

These devices included heart valves, surgical dressings, condoms, stents, disposable hypodermic syringes and orthopaedic implants, among others. RKL ARD

**Source:** *ET Healthworld, 2nd August 2017.*

## No More Freebies: India Plans Crackdown on Marketing by Drugmakers

India, one of the world's largest markets for pharmaceuticals, is drawing up its first set of marketing rules for drugmakers, restricting gifts and trips offered to doctors and pharmacists to 1000 rupees ($15), according to a draft proposal seen by Reuters.

While such rules are common elsewhere in the world and adhered to by large pharmaceutical companies, they are not set in stone in India, where campaigners have long demanded a crackdown on unethical selling practices. These have included gifts ranging from electrical appliances to foreign junkets to encourage doctors and pharmacists to prescribe and stock certain medications.
Currently, India has only a voluntary marketing code that critics say is ineffective.

"In India, corruption and bribery of doctors is widespread," said Samiran Nundy, one of India's leading gastrointestinal surgeons. "I've seen a range of ways in which this works, from presents to doctors to paying for them to attend conferences in places like Thailand."

"It's great that marketing rules are coming into place, but there are a huge number of regulations in India that are not enforced," he added. "I hope that these will be enforced."

Apart from limiting marketing spending, the draft proposal drawn up the Department of Pharmaceuticals and being reviewed by India's law ministry would also forbid drugmakers from making misleading claims around the curative abilities and efficacy of drugs.

The rules also impose strict limitations on the number of trial samples offered to doctors.

An official at the Department of Pharmaceuticals declined to comment on the specifics of the draft, but told Reuters that the order was being reviewed.

The official, who asked not to be named, said no timeline has yet been set on the implementation of the new rules.

According to the draft seen by Reuters, a failure to abide by the rules will result in a marketing ban on a drugmaker for more than a year depending on the degree of the violation, and the confiscation of "all packets of the highest selling brand of drugs" made by that company.

The seized drugs will be handed over for use at government hospitals across the country.

Companies can turn a marketing suspension order into a cash fine, according to the proposal. They will have to pay penalties of between 500,000 rupees ($7,800) and 100,000,000 rupees ($1.56 million) to reverse a marketing suspension order, depending on the severity.

**MANDATORY CODE**

In a letter last year, Tapan Sen, a member of Rajya Sabha, urged the government to act on drafting a mandatory code on the marketing of pharmaceuticals, citing irregular practices by several companies.

Indian media reported that the letter said the country's largest drugmaker, Sun Pharma, Abbott India and privately-held Macleods Pharmaceuticals were among drugmakers found to have sent doctors on "pleasure trips."

Abbott said at the time that it had a strict policy against providing gifts and other incentives to doctors, while Macleods refuted the allegations.

A Sun spokesman told Reuters the company organises 'continuous medical education' programmes to educate doctors, not promote its products, and these are compliant with the voluntary marketing guidelines set by the government in 2015.

The current draft says companies will be allowed to organise screening camps or awareness campaigns at public health centres, but it bars advertising by stealth and mandates that doctors involved in such events be paid commensurate to their average daily income.

To ensure implementation of the rules, an 'Ethics Compliance Officer' of the rank of joint secretary to the Indian government would be appointed.

Pharmaceutical marketing practices have long been a subject of controversy globally. In India, where health insurance is

scarce and many rely on pharmacists for medical advice, critics say sketchy practices have led to the over-prescription of strong cocktail drugs, causing drug-resistance.

GlaxoSmithKline was battered by a bribery scandal in China that landed it with a record $490 million fine in 2014.

It went on to slash the number of sales reps and overhaul its business globally, stopping sales-based incentives for drug reps and reducing paid junkets for doctors.

**Source:** *ET Healthworld, 2nd August 2017*

## Prices of Orthopaedic Implants to be capped

**Data on usage and pricing need to be studied first**

After capping the price of cardiac stents, the National Pharmaceutical Pricing Authority has started work on a similar exercise for orthopaedic implants. As with cardiac stents, implants can have huge margins, ranging from 200% to 500%, making them very expensive for patients and insurers. So expensive, in fact, that some people choose to live in pain or with heavy medication rather than opt for surgery.

The NPPA has had two meetings with stakeholders, including members from the Indian Orthopaedic Association and manufacturing companies, to gather data on the costs of making the implants, landings costs, sale volumes, the number of surgeries of each type across the country. “How does one know what are they doing on the ground level?” NPPA's chairman Bhupendra Singh asks. “There is no standard norm on how much profit they can make. To get clarity, we have started collecting all the data that we can.” The NPPA wants to ensure that it gets pan-India source data without relying on third parties.

**Complex Task**

The sheer variety of implants makes this a very complex task. This complexity is because the human body has 206 bones, ranging from the long thigh bone, to the tiniest, a carpal bone behind the fingers in the hand, and over 700 joints. There are modern implants available to help every bone to knit together after a break or fracture, what the medical world calls 'trauma'. To oversimplify for the layperson, they broadly fall include screws, nails, plates, wires, clips, and there are more than 2000 variations in size, shape and material based on where the implant is needed and what problem it is trying to solve. And then there are joint replacements, including those for the knee, hip, shoulder, elbow, hand, which each has several variations, based on the material used.

Prices vary drastically too. Imported implants are way more expensive than indigenous ones. For example, a cemented hip replacement varies from Rs. 50,000 to Rs. 70,000, while an uncemented one ranges from Rs. 75,000 to Rs. 1.60 lakh. For knees, a cemented implant would range from Rs. 75,000 to Rs. 1.20 lakh, and a state-of-the-art prosthesis that offers better results could go up to Rs. 2.20 lakh.

**Source:** *The Hindu, 3rd August 2017.*

## Unethical Drug Trials: Doctors Facing Charges to Move HC

After the Medical Council of India (MCI) released orders to suspend eight senior doctors of MY Hospital over allegations of unethical drug trials, their fate now lies with MCI's state unit.

The doctors in question have decided to approach the high court seeking a stay against the suspension and are only waiting for the lawyers' strike to come to an end.

Simultaneously, MGM Medical College is looking into other options in case the state body of MCI suspends the doctors.

While Dr VS Pal holds the post of superintendent of MY Hospital, Dr Hemant Jain is superintendent of Chacha Nehru Children Hospital. Dr Anil Bharani and Dr Asheesh Patel are professor and assistant professor respectively in the Medicine Department.

Dr Anil Bharani said, "I only came to know about this information through newspapers and no copy from MCI has reached to me. If I do receive it, I will think about going to court."

Apart from Dr Pal serving as superintendent of Government Mental Hospital, Dr Ujjav Sardesai, Dr Ajay Paliwal and Dr Pali Rastogi are from the psychiatry department. Dr Ram Ghulam Razdan was recently removed from the post of superintendent of Government Mental Hospital after his name surfaced for allegedly giving 'wrong' information to the media about the deaths at MYH due to an alleged shortage of oxygen reported a month ago.

Dr VS Pal said, "I did not receive any official information regarding any action of suspension from MCI. When I receive it, I will decide my further course of action."

The suspension of these doctors, who also take care of administrative work and teach students, will be a matter of great concern for the college administration.

"MCI has instructed the state body of the medical council and now only the action is left. The decision has not been communicated to us," Dean Dr Sharad Thora told TOI.

He added that in case an order is arrived at, the work of the psychiatry department will be affected the most as almost all the doctors will face a three-month suspension.

"In this case, we will seek directions from the state medical council for alternative arrangements so that patients, students and the administrative works will not be affected," Dr Thora said.

**Source:** *ET Healthworld, 5th August 2017*

## GST FAQ: Drugs & Pharmaceuticals

**Question 1:** Whether formulations cleared have to be assessed to GST under transfer price mechanism or on the basis of MRP printed on them?

**Answer:** The assessment of drugs and formulations under GST would be on the basis of transaction value at each level of supply with end to end ITC chain for neutralizing the GST paid at the procurement level.

**Question 2:** What are the requirements for clearance of physician samples distributed free of cost?

**Answer:** In case of clearance of physician samples distributed free of cost, the ITC availed on the said samples has to be reversed in view of the provisions under Section 17(5)(h) of the CGST Act, 2017.No tax is payable on clearance of physician samples distributed free of cost as the value of supply is zero and no credit has been availed.

**Question 3:** What is the procedure for movement of time expired medicines from the retail outlets to the manufacturer for destruction?

**Answer:** In such cases, the manufacturer may issue a credit note within the time specified in sub-section (2) of section 34 of the CGST Act, 2017 subject to the condition that the person returning the expired medicines reduces his ITC. Subsequently, when the time expired goods are destroyed, the manufacturer has to reverse his ITC on account of goods being destroyed. Where the goods are returned after the time limit specified in section 34(2) of the CGST Act, 2017, the registered person returning the goods shall issue a tax invoice, as it is a supply within the meaning of Section 7 of the CGST Act, 2017.

**Question 4:** How loan and licensee units carry out their operations in GST regime?

**Answer:** GST law does not have any special provision for loan and licensee units. Where the contract are in the nature of performance of job-work, these units can opt to follow the procedure laid down in section 143 of the CGST Act, 2017 i.e. the principal can send any inputs etc. to such units without payment of tax and the principal can clear the goods from the premises of such units if the principal declares these units as his additional place of business or where such units are themselves registered under section 25 of CGST Act, 2017.

**Question 5:** What is the treatment of clearances effected to Special Economic Zones?

**Answer:** The clearances effected to the SEZ are zero rated supplies in terms of Section 16 of the IGST Act, 2017. Accordingly, the supplier can claim refund of IGST paid on such supplies or clear the same under bond/ letter of undertaking and claim refund of the unutilised ITC.

**Question 6:** Whether SEZ unit located in a State requires a separate registration under GST?

**Answer:** The SEZ unit located in a State is treated as a business vertical distinct from other units located in the State outside the SEZ [first proviso to Rule 8 of the CGST Rules, 2017 read with Section 25 of the CGST Act, 2017]. Hence, separate registration is required to be obtained for the unit located in SEZ.

**Question 7:** Whether ISD registration is required to be obtained separately?

**Answer:** In terms of second proviso to Rule 8 of the CGST Rules, 2017 read with Section 25 of the GST Act, 2017, every person being an Input Service Distributor has to make a separate application for registration.

**Question 8:** What is the transitional credit that can be availed on the existing stocks held by a registered person under GST, who was not required to be registered under the existing law?

**Answer:** In terms of Rule 117(4) of the CGST Rules, 2017 (transitional provisions) read with Section 140(3) of the CGST Act, 2017, a registered person who was not registered under the existing law and who is not in possession of any document evidencing payment of central excise duty in respect of the goods held in stock, shall be allowed credit at the rate of sixty per cent on such goods which attract central tax at the rate of nine per cent or more and forty per cent for the other goods of the central tax applicable on supply of such goods after 01st July 2017 and the said amount shall be credited in the electronic credit ledger after the central tax payable on such supply has been paid. In case where integrated tax is paid, the amount of ITC would be at the rate of thirty per cent and twenty per cent respectively of integrtaed tax. This facility is available for a maximum period of 6 months from the appointed day (i.e. upto 31st December, 2017) or till the goods are sold out, whichever is earlier.

**Question 9:** Whether a manufacturer can avail deemed credit in respect of transitional stocks on the appointed day in respect of the stocks for which duty paying document is not available?

**Answer:** In terms of the proviso to Section 140(3) of the CGST Act, 2017, the manufacturer is not eligible to avail deemed credit in respect of transitional stocks, for which duty paying document is not available. Such credit is not available in case of SGST except where VAT was payable on the basis of MRP.

**Question 10:** Whether deemed credit is available in respect of goods purchased from tax free zones?

**Answer:** The deemed credit in terms of Rule 117(4) of the CGST Rules, 2017 (transitional provisions) read with Section 140(3) of the CGST Act, 2017 would be available in respect of the goods, which were not unconditionally exempt from the whole of the duty of excise specified in the First Schedule to the Central Excise Tariff Act, 1985 or were not nil rated in the said Schedule. As the goods purchased from tax free zones were exempted from duty payment under a Notification issued under Section 5 of the Central Excise Act, 1944 and not Nil rated in the First Schedule to the Central Excise Tariff Act, 1985, the deemed credit would be available in respect of such goods held in stock on the appointed day.

**Question 11:** What is the obligation cast on the Registered Person in case of purchases from Unregistered Person?

**Answer:** In terms of Section 9(4) of the CGST Act, 2017 read with Section 31(3) ibid, the Registered Person procuring the taxable supplies from an Unregistered Supplier has to raise invoice and pay GST on reverse charge basis in respect of such supplies.

**Question 12:** What is the treatment of supplies made from erstwhile tax free zones?

**Answer:** Since GST is a destination based consumption tax with seamless transfer of ITC credit, no exemptions are accorded to supplies made by erstwhile tax free zones. Accordingly, the goods cleared from erstwhile tax free zones would be subjected to GST from the appointed day (01st July, 2017).

**Question 13:** What is the effect of non-payment of consideration in respect of taxable supplies received by the recipient?

**Answer:** If the recipient fails to pay to the supplier the amount towards the value of supply along with tax payable thereon within a period of one hundred and eighty days from the date of issue of invoice by the supplier, the amount of input tax credit availed proportionate to the amount of consideration not paid would be added to his output tax liability along with interest thereon. The ITC so reversed can be reclaimed by the recipient after payment of consideration along with tax payable there on subsequently. This provision is not applicable in respect of deemed supplies made without consideration in terms of Schedule I to the CGST Act, 2017.

**Question 14:** Whether separate sequence numbers can be maintained for invoices issued by the Registered Person in respect of supplies made under GST?

**Answer:** In terms of Rule 46(b) of the CGST Rules, 2017 single or multiple series of invoices can be raised by the Registered Person for the supplies made under GSTas long as such invoice numbers are unique for a financial year.

**Question 15:** Which is the document required to be issued by the Registered Person for supply of goods from one premises to another premises under the same registration number?

**Answer:** In terms of Rule 55(1)(c) of the CGST Rules, 2017 such movements have to be effected under the cover of a delivery challan along with any other document that may be prescribed in lieu of the e-way bill.

**Question 16:** Whether discounts can be claimed as an abatement from the price for assessing GST?

**Answer:** In terms of Section 15(3) of the CGST Act, 2017, the value of supply for charging GST shall not include any discount which is given before or at the time of the supply if such discount has been duly recorded in the invoice issued in respect of such supply. The value of supply shall also not include any discount which is given after the supply has been effected, if such discount is established in terms of an agreement entered into at or before the time of such supply and specifically linked to relevant invoices and ITC attributable to such discount has been reversed by the recipient of the supply.

**Question 17:** What are the relevant provisions for movement of transitional goods lying at the premises of contract manufacturer on or after appointed day?

**Answer:** The procedure for movement of transitional goods lying at the premises of Contract Manufacturers/ Loan Licencee is governed by the provisions under Section 141(1), (2) & (3) of the CGST Act, 2017.

**Source:** *The Hindu, 6th August 2017*

## Study Says A Steroid Used to Treat Kidney Ailments Has Adverse Effects

A steroid used to treat a kidney disease, common in India, itself causes unacceptable levels of infections among patients, a new study has found and stressed the need to change the existing treatment guidelines.

The study conducted by the George Institute for Global Health found that treatment with pills of methylprednisolone is linked to a large increase in the risk of serious adverse effects such as infections, gastrointestinal and bone disorders among patients with IgA nephropathy and those having excess protein in their urine.

IgA nephropathy is a kidney disease that occurs when the antibody immunoglobulin A (IgA) gets deposited in the kidneys.

"Up to 30 per cent of all people with IgA nephropathy will eventually develop end-stage kidney disease. Decreased kidney function, persistent proteinuria, and hypertension are the strongest risk factors," said Vivekanand Jha, Executive Director -- GIGH India.

Jha is one of the authors associated with the study which was published in the Journal of the Americian Medical Association.

Methylprednisolone is also used to treat conditions like skin diseases, rheumatic disorders, allergies, asthma among others.

In the study, participants with IgA nephropathy and proteinuria (presence of excess proteins in urine) were randomly assigned to oral methylprednisolone for two months, with subsequent weaning over 4 to 6 months.

Recruitment was planned in several countries including China and India but after 2.1 years' median follow-up, it was discontinued because of an unexpectedly high rate of serious adverse effects, including infections, gastrointestinal and bone disorders, it said.

Serious events occurred in 20 participants (14.7 per cent) in the methylprednisolone group vs 4 (3.2 per cent) in the placebo group, mostly due to excess serious infections, including two deaths, the study said.

"Although the results were consistent with potential renal benefit, definitive conclusions about treatment benefit cannot be made, owing to early termination of the trial," says Vlado Perkovic of the George Institute for Global Health, Sydney, and a lead author of the study.

Professor Hong Zhang of Peking University First Hospital, Beijing, added that a limitation of the study was that the recruitment was stopped earlier than planned because of excess adverse events and so the power of the study was less than predicted, and both risks and benefits might be overestimated thus.

India is currently leading global recruitment in the follow up low-dose testing trial which will investigate how the benefit of treatment will be available to the patients without the risk. Eight Indian centres are participating.

"Our effort is to see that the treatment should produce benefit, but with no side effect or risk as was seen in the first phase.

"A series of steps are being taken to mitigate this risk in the second phase - this includes reducing the dose and giving it for slightly longer duration, and use of prophylaxis against the common infections like TB, and lung infections," said Jha.

The George Institute for Global Health works on a broad health landscape and conducts clinical, population and health system research aimed at changing health practice and policy worldwide.

The Institute has been ranked among the top 10 global institutes for impact for the last several years.

**Source:** *ET Healthworld, 6th August 2017.*

## Indian Pharma Market Growth Declines by 2.4% in July 2017 Due to GST Implementation

The Indian Pharmaceutical Market growth declined by 2.4 per cent during the month of July 2017 to Rs. 9,280 crore due to the first month of GST roll out. The operational issues like difficulties in software updation, the stockist billing was hampered to a large extent leading to a decline in market growths for the month of July 2017. Monthly growth has been pulled down by the volumes of the established products. FDC related market show a de-growth of 23.3 per cent while the non FDC market declined by 1.9 per cent.

According to AIOCD Pharmasofttech AWACS Pvt. Ltd report, Anti-infectives sales declined by 15.8 per cent, while dermatology achieved growth of 7 per cent. Gastro Intestinal and Vitamins segments registered decline of 1.9 per cent and 2.3 per cent. However, maaujor chronic therapy like anti-diabetic has shown a positive double digit growth of 12.9 per cent. Cardio segment and CNS posted growth of 4.5 per cent and 1.5 per cent respectively

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Among the top 10 corporates, Intas has the highest growth of 7 per cent followed by Abbott at 4.5 per cent Zydus at 3.3 per cent. Glaxo after few months of positive growth has slipped to a degrowth of 2.5 per cent. 22 corporate from leading top 50 companies registered positive growth. Sun Pharma postfolio showed a degrowth of 2.2 per cent Total 36 companies launched in last 36 months and three companies cross Rs. 10 crore in revenue

The revenues of Indian companies declined by 3.3 per cent during July 2017 while the MNC were stagnant at one per cent months growth. Amongst the top 50 MNCs Boehringer Ingelheim which grew at 17.3 per cent while Eli Lilly was growing at 11.5 per cent followed by Novartis at 10.3 per cent. In the non- NLEM category Indian companies declined at a Rate of 2.1 per cent whereas MNCs grew at 1.9 per cent

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From therapy perspective 11 therapies have shown a positive growth for the months of July 2017. Respiratory market posted a degrowth of 16.2 per cent, Gastro intestiinal market declined at 1.9 per cent, pain & analgesics market also declined at 5.7 per cent. In chronic business, Anti-diabetic market grew at 12.9 per cent and cardiac at 4.5 per cent, Neuro/CNS was stagnant at 1.5 per cent

From regional perspective 9 regions have posted positive growth for month of July 2017. North East market grew the highest at 53.9 per cent followed by North Rajasthan at 20.5 per cent and Mumbai city at 11 per cent. Amoxycillin plus Clavulanic acid market posted a de-growth of 13.6 per cent in July 2017. However, Glimepiride plus Metformin market grew at 5.5 per cent. The market of Paracetamol plain showed a de-growth of 23.7 per cent

Among the recently launched molecule, Azilsartan is now valued at Rs. 29 rore there are 35 brands alrealdy launched. On MAT basis with Zilarbi (Emcure) leading follwed by Aztric (Intas) and Azildac (Zydus. Lulicionazole segment is worth Rs. 144 crore on MAT basis. Total 149 brands and 425 SKUs launched in July 2017 and within the antidiabetic category there are 4 brands launched in the months of July 2017.

**Source:** *Pharmabiz, 14th August 2017*

## India Grants Pfizer Patent for Blockbuster Brand Prevenar 13

India has granted US drug giant Pfizer a patent for its blockbuster vaccine, Prevenar 13, used to protect children against life threatening pneumococcal diseases. The approval comes over a decade after the company applied for the patent in the country. Pneumonia is one of the leading cause of deaths of children under five years of age. India has seven pneumonia related deaths per 1,000 live births, according to the 2016 Pneumonia and Diarrhea Progress Report by John Hopkins Bloomberg School of Public Health.

Prevenar 13 is approved to prevent pneumococcal pneumonia and invasive pneumococcal diseases caused by 13 strains of streptococcus pneumonia, according to Pfizer. The vaccine provides the “broadest” serotype coverage of any pneumococcal conjugate vaccine available in the world today, the company's spokesperson told ET.

Pfizer subsidiary Wyeth's application for grant of Prevenar 13's patent “entered national phase” in October 2007, according to the Indian Patent Office's document that granted the approval. Over the years, this patent application has been opposed by Indian vaccine maker Panacea Biotec and global medical humanitarian organisation Médecins Sans Frontières (MSF).

According to those opposing the application, Pfizer's vaccine lacked the novelty for it to be considered for a patent but the patent office, in its approval on August 11, dismissed these arguments.

According to the office, Pfizer has demonstrated “surprising effects” that have to be considered as establishing that the vaccine is inventive.

“We are pleased to note that the validity of the Prevenar 13 patent has now been recognized by the Indian Patent Office,” a Pfizer spokesperson told ET.

“Supported by extensive clinical research and real-world experience, each dose of PCV 13 requires 400 different raw materials, 580 manufacturing steps, 678 quality tests and two and a half years to produce…Pfizer remains committed towards further enhancing access of this vaccine in India, both in the market as well as through partnership with the Government to expand

introduction in the public program."

Prevenar 13 was launched in India in 2010, according to the spokesperson.

The vaccine has consistently been one of Pfizer's strongest performing brands, experiencing year-on-year growth in the "mid double digits" and capturing 18% of the Indian vaccine market, according to Pfizer's 2016 annual report.

This March, the Indian government introduced Pfizer's PCV 13 vaccine into its national immunisation program through a program funded by Gavi, the Vaccine Alliance. Around five states (approximately 5.15 million babies) are expected to be covered in the first phase.

**Source:** *The Economics Times, 23rd August 2017.*

## Maha FDA Issues Show Cause Notices to Hospitals for Reuse of Catheters, Overcharging Patients

Against the backdrop of increasing number of cases of reuse of catheters across hospitals in Mumbai, Pune and Nashik, Maharashtra Food and Drug Administration (FDA) has flagged this issue with the central government and served show cause notices (SCN) to around 8 corporate hospitals which were involved in the unethical practice of reusing catheters and overcharging patients subsequent to its reuse at the point of care. These hospitals are reported to have charged patients as much as 77% of the retail price

Catheters are used to manage urinary incontinence which includes standard catheter which is a thin, flexible, hollow tube that is inserted through the urethra into the bladder and allows the urine to drain out. A catheter is used for draining a person's bladder and is ordered by a physician for many different medical purposes.

Informs Maharshtra FDA Commissioner Pallavi Darade, "Hospitals have been given 15 days time to reply to the SCNs failing which they will face prosecutions as per the provisions of the law." A letter on the same has also been sent to the central government, state health ministry and state medical education department as well to apprise them of the unethical practice so that a policy decision could be taken forward jointly on the same and actions can be taken based on the current set of rules as provisioned under the law with reference to each department and jurisdictions

After coronary stents, around 14 more medical devices that were rampantly sold at inflated rates in hospitals, could see a price regulation in the coming months. The list includes orthopedic implants, intraocular lenses and artificial heart valves to consumables such as syringes, needles and catheters

The drug pricing regulator National Pharmaceutical Pricing Authority (NPPA) is also planning to collect data on pricing and availability of orthopaedic implants and other medical devices from different sources to help notify their ceiling prices soon.

Against the backdrop of rampant practices of overcharging of coronary stents at the point of care, NPPA had fixed prices of coronary

after bringing it under National List of Essential Medicines (NLEM) following adverse market reports of unethical markups at every stage of the supply chain

Maharashtra FDA had in the past seized orthopaedic implants worth Rs. 2.31 crore from a Mumbai based manufacturer who was manufacturing, stocking and supplying products in a clandestine manner without a license. The implants were illegally manufactured, stocked and supplied in Bhiwandi in violation of Drugs and Cosmetic Rules. Further to this, orthopaedic implants were also seized from Akola worth Rs. 4.40 lakhs

Orthopaedic implants is one such product which is subject to unethical markups in the supply chain and it has been given to understand and patients are fleeced at the point of care through the hospital - dealer nexus.

Section 18(c) prohibits stock, distribute and sale of the medical devices, except Licence issued under Drugs and Cosmetics Rules, 1945. This is an offence attracting penalty of imprisonment of 3 to 5 years and fine of minimum Rs. 1 lakh, as prescribed under Section 27(b)(ii) of the said Rules.

**Source:** *Pharmabiz, 23rd August 2017*

## Abbot withdraws Absorbable Stent, Makes No Mention of Safety Concerns

Abbott has globally halted the sale of its bioresorbable cardiac stent Absorb, ostensibly due to "low commercial sales". Its statement announcing this on Friday had no reference to how sales had fallen drastically due to safety concerns.

Before stent prices were capped in India earlier this year, Indians were paying more than twice as much as European and US consumers for Absorb. Also, Absorb sold here at a huge premium over normal drug eluting stents despite trials conducted abroad showing increased risk of heart attack and patients having to be put on blood-thinning drugs for longer with these so-called superior stents. These results led several countries to restrict the use of Absorb to only clinical trial sites.

A few cardiologists in India, closely identified with promoting these stents, had opposed price control of bioresorbable stents, which sold at about Rs 1.9 lakh before the Rs 31,000 cap imposed by the drug pricing authority. In the US, the price was about $1,500 or about Rs 1 lakh and in Europe it was even lower at about 900 euros. The use of bioresorbable stents in India was more than five times as high as in developed countries, but there has been no investigation into the safety of patients implanted with these devices.

Given the poor uptake of Abbott's bioresorbable stents and safety concerns regarding these surfacing in the US, Canada, Australia and the European Union, the National Pharmaceutical Pricing Authority (NPPA) recommended allowing the company to withdraw these stents from the market. However, the Central Drug Standards Control Authority (CDSCO), meant to safeguard patient interests and ensure the safety of drugs and devices, did not suspend the commercial use of the Absorb as most

countries had done. CDSCO issued a device alert regarding Absorb warning about increased risk of major cardiac events including cardiac death, heart attack or additional procedure to re-open the treated heart vessel. Yet, it left it to patients and doctors to report any adverse events though there is no proper mechanism for reporting such events or collecting information on them, especially for devices.

Abbott had filed an application for withdrawal of Absorb soon after price control claiming it was not commercially viable at the controlled price but said nothing about safety concerns. Absorb was less than 1% of Abbott's global stent sales, which shrunk further with the restrictions.

After ordering all stent companies to maintain their stocks for six months following price control in February, NPPA asked them to submit weekly reports on stent production/import and distribution. Based on the data submitted, the NPPA found that the share of the three multinational companies, which was about 70-80%, remained at about 65% even after the price cap. In the case of Absorb, the data showed that there was hardly any import and no movement of stocks from May to July.

Bioresorbable stents, which prop open the artery and eventually gets absorbed into the body are considered to be the technology of the future. A few companies other than Abbott too have brought in bioresorbable stents into the market. Abbott too is said to be working on a next generation bioresorbable device.

**Source:** *Times of India, 10th September 2017.*

## Pharma Majors Knock at Niti Aayog's Doors with Concerns over New Drug Policy

Drug industry lobby groups have reached out to Niti Aayog with their apprehensions and suggestions in the hope that their message will reach the Prime Minister's Office.

Indian drug companies have approached the government's think tank Niti Aayog, seeking some changes in the recently floated draft drug pricing policy, industry insiders said.

Drug industry lobby groups such as Indian Pharmaceutical Alliance, Indian Drug Manufacturers Association and The Federation of Pharma Entrepreneurs have reached out to National Institution for Transforming India (Niti Aayog) with their apprehensions and suggestions in the hope that their message will reach the Prime Minister's Office (PMO).

They hope that Prime Minister Narendra Modi can offer some tweaks that would take in account industry's concerns over some key issues that they said the draft policy prepared by the department of pharmaceuticals has overlooked, industry insiders said.

Members of Niti Aayog are expected to meet the PMO with the industry's concerns this week, they said.

The Rs 98,000-crore drug industry has mainly objected to three proposals in the draft policy floated last month: one drug one brand, curbing retailer margins, and mandatory

bioavailability and bioequivalence (BA/BE) test for all drugs approved by state regulators and also future renewals.

The industry said the move to restrict companies from using different brand names for drugs with same active ingredient would affect the marketing reach and business prospects of drug companies. Having different brand names gives accountability to the sales force, and doctors also prefer brand names to identify a product with appropriate therapeutic benefit, companies said.

"Abolition of brand names for single ingredient drugs will in fact discourage innovation as companies will be denied option to distinguish an innovative generic product from me-too generics," Indian Pharmaceutical Alliance (IPA) said in its written note to Niti Aayog.

"To be credible, the policy should cite evidence to support its observation that "giving brand names to generic drugs hampers real innovation," it said. ET reviewed a copy of IPA's letter.

Drug companies have also objected to mandatory quality control BA/BE tests for all drugs, including for future renewals of manufacturing licenses.

Companies say the government should first establish ample BA/BE study centres and provide relevant infrastructure before introducting these requirements.

**Source:** *The Economic Times, 25th September 2017.*

## TRYING AND TESTING

**What You Should Know Before You Opt for A Clinical Trial so You Have The Safest Experience Possible**

Clinical trials in India have got a bad rap, but things are changing, say doctors and scientists who lead them. "Think of scientific research as something for the greater good of humankind; something that benefits society, even if not immediately, then in the generations to come," says Professor Thangarajan Rajkumar, head of the Molecular Oncology department at Adyar Cancer Institute, Chennai. He speaks with reference to clinical trials in India, and our reluctance to be a part of them, perhaps partly because of our country's history of corruption with regard to them and partly because there are no sure-shot results.

"India now has one of the most streamlined systems of research, with strict ethics committees and a vigilant Drugs Controller General of India (DCGI)," says Dr Pooja Sharma, Senior Scientist at Medanta Institute of Education and Research, and founder of PARTAKE, Gurgaon, a patient education programme.

Colin Gonsalves, founder of the Human Rights Law Network (HRLN), disagrees vehemently, especially in cases where people see no way out and cannot afford treatment.

He speaks of unconscionability, when a legal contract is tilted against a vulnerable party, in this case, the patient. He hopes to see the nexus between pharma companies and the medical fraternity broken.

As long as clinical trials are allowed in India though, it is worth knowing a few basics if you are offered one.

All trials are listed either on the Clinical Trial Registry (clinicaltrials.gov), a resource provided by the US National Library of Medicine or on the Clinical Trials Registry – India (ctri.nic.in). Every trial has a number you can identify it with.

Trials are of two types: investigator-origin trials and pharma- or medical-device-driven ones. The former is led by an institution/clinician and could be funded by the institution itself or by a government agency. In the latter, research is designed by the company, the clinicians are chosen by them and the team of researchers are given a fee by them. Bilateral agencies may also fund certain trials, and these may be done through the government or certain NGOs.

Informed consent is at the heart of enrolment, so it is the participant's right to know of every aspect of the trial. There is a 16-point check-list for this, including letting the patient know of the nature of the research, what the study is about, what it hopes to prove, what previous studies say on the subject, risks, possible benefits, compensation (life and disability insurance, travel allowance, compensation for loss of wages).

There is a confidentiality clause that does not allow the person's name to be disclosed. A person can opt out of any study at any point in the process without being penalised and can continue to have the standard of care treatment provided.

All expenses of the medical treatment are borne by the funding agency, including toxicity management (either due to the new drug or the standard of care, like chemo).

Every trial will have to be approved by a government-recognised ethics committee, consisting of an amalgam of people, ranging from clinicians, priests, lawyers, sociologists and social workers. This body of people is available for the person enrolled in the study. They also monitor the trial and will take a call on compensation in case of any adverse event.

**Questions to ask**

**If you or anyone you know is offered a trial, ask these questions and insist on the answers in writing. You may also choose to run it by a lawyer.**

What is the drug/device and what is it meant for?

Has the drug/device been tested abroad or anywhere else in the country?

What phase is the trial at?

What are the possible adverse effects?

What is the standard line of treatment? (Some diseases may not have this).

Why am I being offered this trial if there are already best practices in place?

Is it going to be a placebo trial and will treatment given be as per current standards?

Is the new drug/approach in addition to the standard line of treatment?

What is the cure rate with the standard line of treatment and will the new medicine enhance it (if there is some data on this)?

Will it reduce the time spent in the hospital (in case of a procedure/modality)?

By joining the trial, what is the level of toxicity I will be exposed to, and how will it impact my life? Will the benefit be greater than the toxicity?

Is it possible to withdraw from the trial without compromising treatment?

Who will the agreement be with? (It should be with the funding agency, not an intermediary).

Who is the sponsor? Who is the principal investigator? Which is the institution that the research is taking place?

Is there is an insurance policy in place and what are its terms?

**Source:** *The Hindu, 2nd October 2017.*

## USFDA Approves First Test to Screen Zika Virus in Donated Blood

The U.S. Food and Drug Administration (FDA) has approved for the first time a test for detecting the Zika virus in donated blood.

The Zika virus is transmitted primarily by mosquitos (Aedes aegypti), but it can also spread through blood transfusion and sexual contact.

The cobas Zika test, manufactured by Roche Molecular Systems Inc., is intended for use by blood collection establishments to detect Zika virus in blood donations, not for the individual diagnosis of Zika virus infection, the FDA said.

"Screening blood donations for the Zika virus is critical to preventing infected donations from entering the U.S. blood supply," Peter Marks, Director of the FDA's Centre for Biologics Evaluation and Research.

The test is a qualitative nucleic acid test for the detection of Zika virus RNA in individual plasma specimens obtained from volunteer donors of whole blood and blood components, and from living organ donors.

The test's clinical specificity was evaluated by testing individual samples from blood donations at five external laboratory sites, resulting in clinical specificity of more than 99 per cent.

**Source:** *The Hindu, 7th October 2017*

## Drug Makers May Have to Declare 'Ex-Factory' Price on Medicine Packs

With a view to bring transparency in drug pricing, the government plans to make it mandatory for pharmaceutical companies to disclose the MRP as well as a medicine's 'ex factory' price on its packs of medicines.

The proposal has perturbed pharmaceutical companies as it will put their manufacturing cost and profit margins in the public domain — elements considered part of their business strategy.

The health ministry has prepared a notification, suggesting changes to the Drugs and Cosmetics Rules which, once approved, would mean drug-makers will have to declare

the price at which the medicine is manufactured exclusive of taxes and all other costs, including logistics, trade margins and other marketing expenses etc.

The notification is likely to be issued soon for comments from stakeholders, an official said.

The industry is concerned that declaring the ex-factory cost on packs will not only put them at a disadvantage by giving away the manufacturing cost to global players, but also create a trust deficit among the general public, who may not understand the nuances behind the gap between ex-factory and retail prices.

"This is a meaningless move by the government as it will not serve any purpose but only project the industry in a poor light. The layman, who does not understand the difference between the two, would assume that the industry is cheating with such a high MRP," said DG Shah, secretary general, Indian Pharmaceutical Alliance.

In general, the difference between the ex-factory cost and MRP is huge. Especially, in cases of contract manufacturing – which is very common in India- the gap is often significantly high .This is because the ex-factory price reflects only the manufacturing cost to take the product to the market . Officials say the move is aimed at primarily controlling profit and trade margins and bring in more awareness among consumers to enable them to make an informed choice. However, the Indian drug manufacturing industry, already feeling the pinch of price cap etc, feel any such move may mean "death of the industry".

The domestic pharmaceutical retail market is currently pegged at over Rs 1lakh crore. In 2014 , when the government had brought in the existing drug pricing regime , 17% of the industry by volume was under price control. However, with more stringent norms and caps, the purview of price control increased to 24 % by December 2016, industry estimates show.

**Source:** *Times of India, 10th October 2017.*

## Trump Promises Action on Drug Prices that may Impact India

US President Donald Trump has promised to bring the cost of prescription drugs way down and let other countries pay more for these medicines in a new policy that could have implications for India.

He told his Cabinet members at a meeting at the White House yesterday that the prices of prescription drugs in the US have gone through the roof.

"If you look at the same drug by the same exact company made in the same exact box and sold some place else sometimes it's a fraction of what we pay in this country," he said.

Trump did not mention any country, but his policy on prescription drugs, which was discussed during his Cabinet meeting could have implications for India.

This is because for instance, early this year India's National Pharmaceutical Pricing Authority (NPPA) fixed the price of drug eluting stents at USD 450 and bare metal stents at USD 110.

NPAA has said that it intends to take similar measures for other costly medical devices.

"The world as usual has taken advantage of the United States. They are setting prices in other countries and we are not. The drug companies frankly are getting away with murder," Trump said in his opening remarks.

"We want to bring prices down to whatever the other countries are paying or at least close to that," he said.

"They (other countries) are setting such low prices that we're actually subsidising other countries. And that's just not going to happen anymore," Trump said.

"This has been going on for years where our people are paying so much more. I don't mean they are paying two per cent more. They are paying double, triple, quadruple. They are paying so much more that it is very unfair to the United States as usual," Trump said.

**Source:** *ET Healthworld, 17th October 2017.*

## Price Control Didn't Hit Medicine Availability

Stringent government-mandated price control has not affected availability of essential medicines as retail data showed that sales of such items registered over two-fold growth in the pharma market.

While the domestic pharma market grew by 3% between 2015 and 2016, sales of products under the National List of Essential Medicines (NLEM) grew by 7% in terms of volume in the same period, Pharmatrac AIOCD (All India Organisation of Chemists and Druggists) data compiled through retail sales at chemists and pharmacists has showed.

Prices of medicines listed under NLEM are capped by the government through the National Pharmaceutical Pricing Authority (NPPA).

Not just sales, but the share of price-controlled drugs in the pharma market also increased to 24% by the end of 2016 from 17% in June 2014 on a monthly basis.

The data is welcome news to policy planners as it allays concerns that firms could curtail production or discontinue drugs under price control, thereby defeating the government's objective of making medicines more affordable.

In 2015, the health ministry revised NLEM to add over 100 medicines, expanding the purview of price control. In early 2016, the government brought critical medical devices, including coronary stents, under the list.

“The use of medicines listed in NLEM has risen sharply, fulfilling major objectives of the DPCO (Drug Price Control Order), 2013, and NLEM, 2015. It is obvious that the industry has not shied away from manufacturing or supplying NLEM products,” said D G Shah, secretary general, Indian Pharmaceutical Alliance.

Experts said a few drugs whose margins were severely impacted and volumes were low might see reduced availability but overall, data indicated that price control had increased accessibility while maintaining viability.

“Prices are capped based on a formula which takes care of margins for all supply chain stakeholders. We also ask companies to

produce data if they are affected. There are provisions for revision if margins are hit," an official said, adding the government and the regulator were monitoring data.

The data showed that even in terms of value, the growth in sales of price-controlled medicines on a monthly basis surpassed that of the pharma market. In June 2014, price controlled drugs worth Rs 789 crore were sold, which grew to Rs 1,368 crore in December 2016 — a rise of 73%.

On the other hand, the overall Indian pharmaceutical market, which includes medicines outside price control, recorded a growth of 38% from Rs 6,636 crore in June 2014 to Rs 9,132 crore in December 2016.

However, annual data in terms of value showed a growth of 5% in case of products under NLEM between December 2015 and December 2016, whereas the overall market grew at 12% in the same period. This may be indicative of MRPs coming down, a source said. Total sales of India's local pharmaceutical market is pegged at over Rs 1 lakh crore, of which price-controlled drugs contribute around 16%.

**Source:** *Times of India, 23rd October 2017*

## Popular Antacid Samples Fail Quality Tests, Company Claims they Were Counterfeits

India's apex drug regulator has flagged Indian drug major Sun Pharma's popular medicine brands'Pantocid' and 'Pantocid DSR' for failing quality tests last month. At the same time, the firm claims the samples of these brands that were tested by the regulator were fake imitations of its products.

Batches of the two antacids have figured in an alert listing 22 medicine brands with samples found sub-standard by the Central Drugs Standard Control Organisation (CDSCO), the highest authority on medicine quality in India.

The Pantocid and Pantocid DSR tested by CDSCO were not manufactured by Sun Pharma, the official spokesperson for the Mumbai-based drug maker said.

"They were counterfeit medicines, this has been verified by additional testing and also an on-site visit by a joint audit conducted by Drug Control Department and the Sikkim State FDA," the person told ET.

Pantocid is used to treat acid-related diseases of the stomach and intestine, while Pantocid DSR is primarily used for acidity, nausea and vomiting. Both brands have the second largest share of their respective categories, according to pharmaceutical market research company AIOCD PharmaTrac.

Counterfeit medicines are fake copies of a genuine product. They fall under a category of substandard drugs called SSFFC (substandard/spurious/falsely-labelled / falsified / counterfeit).

The samples of the brands in question failed dissolution and assay tests, according to CDSCO's latest drug alert published this week.

Sun Pharma has requested CDSCO to remove the two brands from its latest drug alert because the entries "are misleading," according to the spokesperson. "At Sun,

quality and safety of our products is non-negotiable," stated the person, adding the company protects its products against counterfeits by working with central and state drug regulators.

Findings of a government survey conducted between 2014 and 2016 to check the proportion of substandard drugs in India had found 3.16% of the samples it tested to be sub-standard, while 0.02% were spurious.

Another prominent brand CDSCO has issued an alert on this month is 'Clop' (30gm), Ahmedabad-headquartered Zydus Cadila's topical cream for allegic disorders. Samples of this cream have failed assay tests, which are carried out to determine the ingredients and quality of the product.

The regulator's latest alert also includes medicines used by patients with diabetes and high blood pressure. For instance, samples of hypertension and chest pain medicine brand 'Amtas-AT 25' by Ahmedabad-based Intas Pharmaceuticals have also failed assay tests.

ET is still awaiting responses from Intas and Zydus Cadila on the regulator's findings
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Pantocid (40 mg) captures nearly 20% of the Rs 627.3 crore pantoprazole market, while its 20mg tablets has nearly 2%, according to PharmaTrac. Pantocid DSR captures over 16% of the Rs 769.5 crore domperidone + pantoprazole market.

Zydus' Clop has the third largest share of the Rs49.2 crore clobetasol market at a little over 8%, according to the research firm.

Intas' Amtas-AT 25 figures in the top 10 atenolol+amlodipine brands, with its 50/5 mg tablets holding 3.34% and its 25/5mg tablets nearly 1% of the Rs469.1 crore market, shows data from PharmaTrac.

**Source:** *ET Healthworld 18th October 2017*

# EVENTS

## INAUGURATION OF IPA-SALEM LOCAL BRANCH


Prof. K. Chinnaswamy, President, Tamilnadu State Pharmacy Council, Chief Guest inaugurated IPA Salem Local Branch on 01.07.2017 at Vinayaka Missions College of Pharmacy, Salem. Thiru. J. Jayaseelan, Vice-President, IPA-Tamil Nadu branch was the Guest of Honour. Dr. V. R. Rajendran, Vice-Chancellor, Vinayaka Missions University presided over the function, Dr. B. Jaykar, President of IPA-Salem local branch and Registrar, Vinayaka Missions University felicitated the function.

During this function a one day Seminar on "Advances in Cell-Based Screening in Drug Discovery and Development". Dr. R. Vadivelan, Prof, JSS college of Pharmacy Ooty, Dr. R. Sowmiya, Director, Greensmedlabs, Chennai and Dr. Karthi Natesan, Chonbuk National University, South Korea were the resource persons and delivered the lectures on cell based screening of drugs. Around 200 delegates from various pharmacy colleges and life science courses were participated in this program. Prof. Dr. R. Kothai, Dept. of Pharmacology proposed vote of thanks.

## PHARMACIST DAY CELEBRATION

The world Pharmacist Day was celebrated on 25th September 2017 by IPA TN branch. During this programme an awareness programme on the subject of "Your Pharmacist is at your service" was organised at various places in and around Chennai city like Marina Beach, Besent Nagar Beach, Anna Nagar, Ashok Nagar, Old Mahabalipuram Road, Tambaram, Perambur and Puducheery. The celebration concluded with valedictory function at Hotel Savera, Chennai. Dr. D. Natarajan, Pharma Consultant, gave a lecture about the role of Pharmacist in development of medicinal plant and various system of medicines like Ayurveda, Siddha and Unani.

Further at Faculty of Pharmacy at Dr MGR Medical University, Maduravoyal, Chennai. Mr. M. M. Yousuf the past president IPA (TN) and Dr. hari Krishnan, Principal of the College organised a gathering to highlight, the Role of Pharmacist and their important in Research area of Healthcare. The function was attended by the president of the University Mr. E. V.S Arun Kumar, Mr. K. Ravi Kumar, Secretary and Dr. Shanwas Khan, Medical Director.



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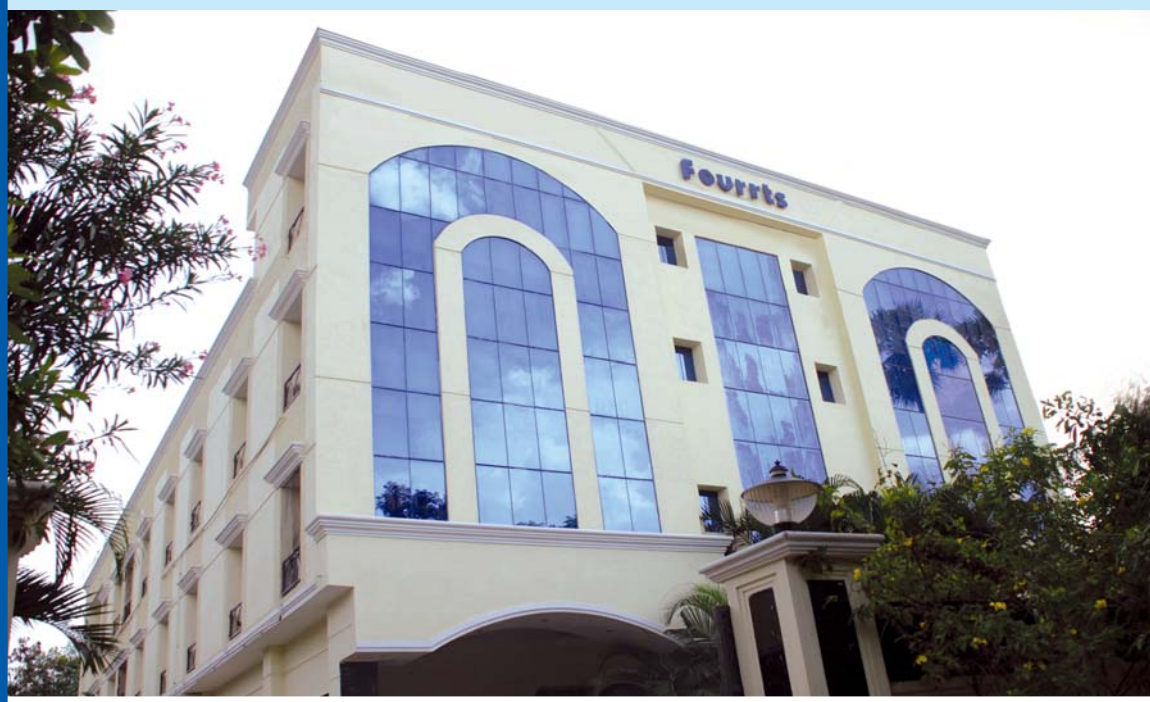


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