



Pharmacovigilance and Adverse Drug Reaction (ADR): A case study

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ABSTRACT

World Health Organization (WHO) and Uppsala Monitoring Centre (UMC) work with and provide technical support to more than 94 countries worldwide. Several disasters led to an awareness that drugs not only can heal but also can harm including sudden death caused by chloroform anaesthesia in 1877 and fatal hepatic necrosis due to arsenicals in 1922. In the United States a tragic mistake in the formulation of a children's syrup in the late 1930s was the trigger for setting up the product authorization system under the Food and Drug Administration (FDA). The Food and Drug Administration had the authority to review new drugs for safety, by scrutinizing animal studies and small human volunteer trials for any signs of serious hazards. In order to prevent unnecessary suffering by patients and to decrease the financial loss sustained by the patient due to the inappropriate or unsafe use of medicines, it is essential that a monitoring system for the safety of medicines in Country is supported by doctors, pharmacists, nurses and other health professionals in the country. The Drug Regulatory Authority (DRA) and National Pharmacovigilance programme, adverse reactions should be reported on a daily basis. A case study has done on the basis of Adverse Drugs Reaction in Chandigarh. The patient was named Pratigya Choudhary, age four year six months old. Prescription of Amoxicillin and Potassium Clavulanate combination given to patient and found Jaundice after two dosages. The patient was serious to admit in Hospital. The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

Key Words: Pharmacovigilance, Adverse Drugs Reaction, Jaundice, Combinational Therapies

1. INTRODUCTION

Pharmacovigilance was developed to measure the safety of medicine. To measure the adverse effect and problems caused by medicine. Pharmacovigilance is the Science and activities related to the detection assessment, prevention of adverse effects or any other drugs related problem.

Vigilance :-

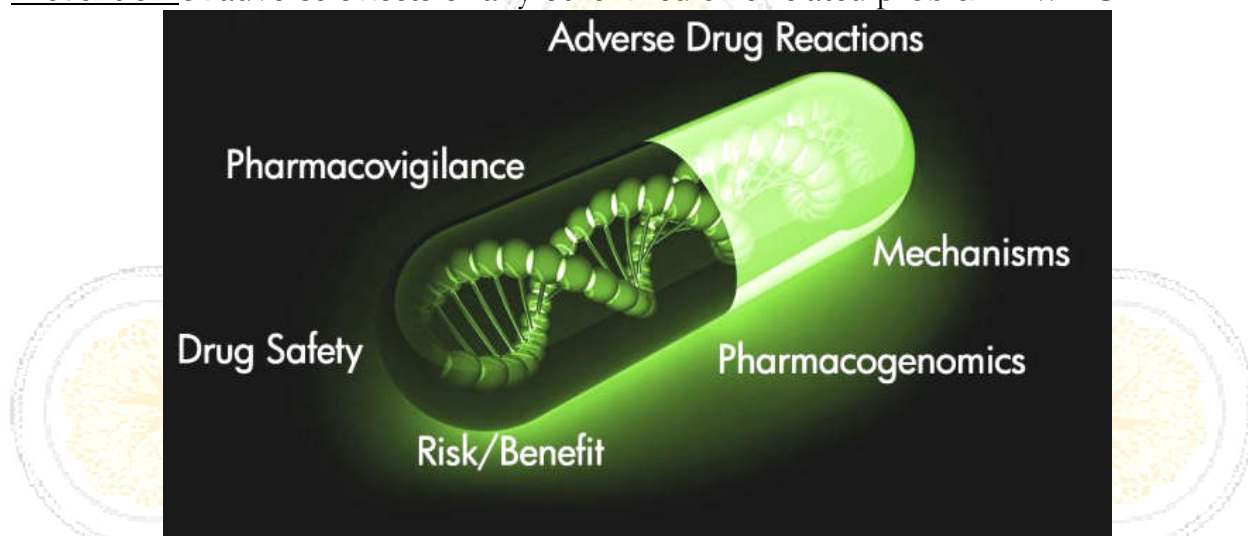
Vigil are = to watch (The process of paying close and Continuous attention).

WHO definition:-

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

Pharmacovigilance :-

The science and activities relating to the Detection, Assessment, Understanding and Prevention of adverse effects or any other medicine-related problem - WHO¹⁻².



Objectives :-

- a) To monitor Adverse Drug Reactions (ADRs) in Indian population.
- b) To create awareness amongst health care professionals about the importance of ADR reporting in India.
- c) To monitor benefit-risk profile of medicines.
- d) Generate independent, evidence based recommendations on the safety of medicines.
- e) Support the CDSCO for formulating safety related regulatory decisions for medicines.
- f) Communicate findings with all key stakeholders.
- g) Create a national centre of excellence at par with global drug safety monitoring standards.

Aims and Responsibilities of PVG :-

- a) Early detection of unknown safety problems
- b) Detection of increases in frequency
- c) Identification of risk factors
- d) Quantifying risks

- e) Preventing patients/Public from being affected unnecessarily
- f) Standard Requirements:
- g) Reporting
- h) Labelling
- i) Approach (Insert, package, etc)

Need of Pharmacovigilance :-

Limited value of animal experiments in predicting human safety Clinical trials are limited in time and number of individuals (a few hundred), usually under favourable conditions, i.e. in the hospital, under close surveillance, over a short period, with few concomitant medications, and with few high-risk individuals (e.g. children, older individuals, pregnant women, or patients with renal or hepatic failure)

Populations not studied in the pre-approval phase:-

- a) Children
- b) The elderly
- c) Pregnant or lactating women
- d) Patients with co-morbidity such as hepatic or renal disorders
- e) Sup-populations carrying known and relevant genetic polymorphisms
- f) Patients of different racial and/or ethnic origins
- g) Rare or delayed serious reactions are likely to remain unnoticed
- h) Rare ADRs (occurring for instance in 1/1000 individuals) are unlikely
- i) To be identified in pre-marketing studies. Effects that is difficult, even impossible to detect clinically:
 - i. Toxicity to Reproduction
 - ii. Genotoxicity
 - iii. Carcinogenicity
- j) A drug that belongs to a widely used pharmacological class may be used in up to 100,000 individuals within the first month, so that a rare but serious ADR may occur only in few patients³⁻⁴.

2. IMPORTANCE OF PHARMACOVIGILANCE

When a medicine is released onto the market there is still a great deal that is Unknown about the safety of the product. Once marketed the medicines are used by Patients who have many different diseases, who are using several other drugs and who have different traditions and diets which may affect the way in which they react to a medicine. Different brands of medicines may differ in the manner in which they are produced and the ingredients that are used. The adverse drug reactions and poisonings associated with traditional and herbal remedies also need to be monitored in each country. The information we receive on the adverse effects of drugs in other countries may not be relevant or applicable to (*Country*)'s citizens. In some cases, adverse effects to certain drugs may only occur in (*Country*)'s citizens. In order to

prevent unnecessary suffering by patients and to decrease the financial loss sustained by the patient due to the inappropriate or unsafe use of medicines, it is essential that a monitoring system for the safety of medicines in {Country} is supported by doctors, pharmacists, nurses and other health professionals in the country. The Drug Regulatory Authority and the Department of Health's Essential Drug Programme are committed to improving drug safety through adverse drug reaction monitoring in {Country}. Through the {Drug Regulatory Authority}'s national Pharmacovigilance programme, adverse reactions should be reported on a daily basis⁵⁻⁹.

- 1) Drug monitoring
- 2) Pharmaceutical preparations - adverse effects
- 3) Adverse drug reaction reporting
- 4) Product surveillance, Post marketing
- 5) Legislation, Drug I. Series



Prescription

3. PHARMACOVIGILANCE STRUCTURE IN INDIA¹⁰

The Pharmacovigilance Programme of India is administered and monitored by the following two committees.

- 1) Steering Committee
- 2) Strategic Advisory Committee

Technical support will be provided by the following committees:

- 1) Signal Review Panel
- 2) Core Training Panel
- 3) Quality Review Panel

Steering Committee:-

| |
|--|
| Pharmacovigilance Programme of India |
| Chairman |
| Drugs Controller General (India), New Delhi, <i>ex-officio</i> |
| Members |

1. Scientific Director, Indian Pharmacopoeia Commission, Ghaziabad, ex-officio
2. Head of Department, Pharmacology, AIIMS, ex - officio
3. Nominee of Director General, ICMR, ex-officio
4. Assistant Director General (Extended Programme of Immunization [ADG(EPI)] as representative of Directorate General Health Services
5. Under Secretary (Drugs Control) as representative of The Ministry of Health & family Welfare.
6. Nominee of Vice Chancellor of Medical/Pharmacy University, ex-officio
7. Nominee of the Medical Council of India, ex-officio
8. Nominee of Pharmacy Council of India, ex-officio

Member Secretary

Officer-in-Charge (New Drugs), CDSCO, New Delhi, *ex-officio*

PARTNERS OF PHARMACOVIGILANCE:-

A complex and vital relationship exists between a wide range of partners in the practice of drug safety monitoring. These partners must jointly anticipate, understand and respond to the continually increasing demands and expectations of the public, health administrators, policy officials, politicians and health professional.

The WHO Quality Assurance and Safety:- Medicines Team

The Quality Assurance and Safety: Medicines team is responsible for providing guidance and support to countries on drug safety matters. The team is part of the Department of Essential Drugs and Medicines Policy, within the WHO Health Technology and Pharmaceuticals cluster.

The purpose of the department is: *To help save lives and improve health by closing the huge gap between the potential that essential drugs have to offer and the reality that for millions of people – particularly the poor and disadvantaged – medicines are unavailable, unaffordable, unsafe or improperly used.*

WHO works towards fulfilling this mission by providing global guidance on essential Drugs and medicines, and working with countries to implement national drug policies.

These are designed to ensure:

- a) Equity of access to essential drugs.
- b) Drug quality and safety.
- c) Rational use of drugs.

To ensure the quality, safety and efficacy of all medicines by strengthening and putting into practice regulatory and quality assurance standards.

The Uppsala Monitoring Centre:-

The principal function of *the* Uppsala Monitoring Centre is to manage the international database of ADR reports received from National Centres. In 2002 this database held nearly three million case reports. The majority of national contributing centres have easy electronic access to these. *the* UMC has established standardized

reporting by all National Centres and has facilitated communication between countries to promote rapid identification of signal¹¹⁻¹⁵.

An international advisory panel of clinical experts determines the validity and clinical importance of the signals generated.

WHO and UMC work with and/or provide technical support to more than 94 countries worldwide. The long term objective of the PvPI is to establish a **'Centre of Excellence'** for Pharmacovigilance in India. To achieve this objective, the PvPI National Coordinating Centre will collaborate with the WHO Collaborating Centre - Uppsala Monitoring Centre (UMC) based in Sweden.

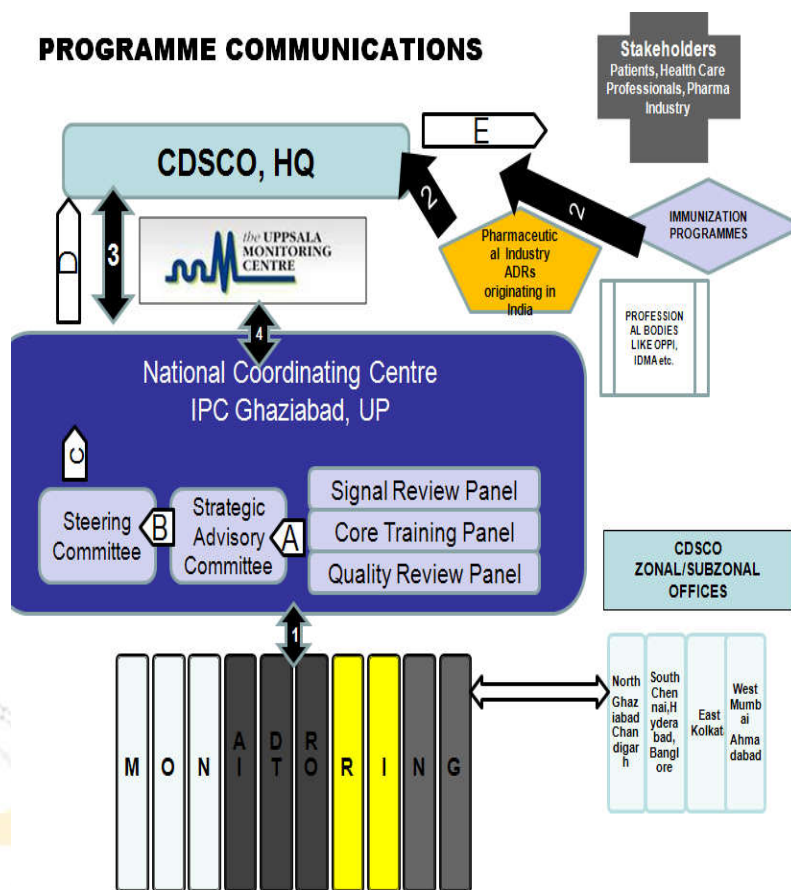
- a) Training of the staff at the PvPI national coordinating centre at IPC *Ghaziabad*, the ADR Monitoring centers in medical colleges across the country.
- b) Usage of UMC's Vigi flow software (for medicines) and Pani flow (for vaccines) at no cost to PvPI.
- c) Access to Vigi base, which contains worldwide medicines safety data
- d) Access to early information about potential safety hazards of medicines (worldwide data).
- e) Technical collaboration for Pharmacovigilance Programme of India.
- f) Technical collaboration for a regular publication that will be issued by the PvPI National Coordinating Centre for distribution to the ADR Monitoring centers and other stakeholders.

CDSKO Headquarters has held several meetings with UMC over the past few years to discuss the potential role and approach for technical collaboration.

4. PHARMACOVIGILANCE COMMUNICATION IN NATIONAL AND INTERNATIONAL LEVEL¹⁰⁻¹¹



PROGRAMME COMMUNICATIONS



Functions of the stakeholders in the PvPI Programme¹⁰⁻¹¹

| Functions of the Stakeholders | |
|--|---|
| PvPI ADR Monitoring Centre in Medical College (PvPI AMCs) | <ul style="list-style-type: none"> • Collection of ADR reports • Perform follow up with the complainant to check completeness as per SOPs • Data entry into Vigiflow • Reporting to PvPI National Coordinating Centre (PvPI NCC) through Vigiflow with the source data (original) attached with each ADR case • Training/ sensitization/ feedback to physicians through newsletters circulated by the PvPI NCC |
| PvPI ADR Monitoring Centre other than medical colleges [Corporate hospitals, autonomous institutes, Pharmaceutical industry, public health programmes] | <ul style="list-style-type: none"> • Collection of ADR reports • Perform follow up with the complainant to check completeness as per SOPs • Report the data to CDSCO HQ |

| | |
|--|--|
| PvPI National Coordinating Centre (PvPI NCC , IPC Ghaziabad) | <ul style="list-style-type: none"> • Preparation of SOPs, guidance documents & training manuals • Data collation, Cross-check completeness, Causality Assessment etc as per SOPs • Conduct Training workshops of all enrolled centers • Publication of Medicines Safety Newsletter • Reporting to CDSCO Headquarters • Analysis of the PMS, PSUR, AEFI data received from CDSCO HQ |
| ZONAL/Sub zonal CDSCO Offices | <ul style="list-style-type: none"> • Provide procurement, financial and administrative support to ADR monitoring centers • Report to CDSCO HQ |
| CDSCO, HQ, New Delhi | <ul style="list-style-type: none"> • Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC at IPC Ghaziabad. • Propagation of medicine safety related decisions to stakeholders • Collaboration with WHO-Uppsala Monitoring Center - Sweden • Provide for budgetary provisions & administrative support to run National PvPI |

5. ADVERSE DRUG REACTION

Adverse drug reaction (abbreviated ADR) is an expression that describes harm associated with the use of given medication at a normal dosage during normal use. ADRs may occur following a single dose or prolonged administration of a Drug or result from the combination of two or more drugs. The study of ADRs is the concern of the field known as Pharmacovigilance. An adverse drug event (abbreviated ADE) refers to any injury caused by the drug (at normal dosage and/or due to overdose) and any harm associated with the use of the drug (e.g. discontinuation of drug therapy).

The World Health Organization defines:

an adverse drug reaction (ADR) as any noxious, unintentional, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. Numerous organizations have their own definition.

Any drug may cause an adverse drug reaction. Undoubtedly, all drugs produce an ADR in someone who has used them.

Three to five percent (3-5%) of hospital admissions are caused by ADRs.

The incidence of serious and fatal adverse reactions in hospital patients has been reported between 0.32% and 6.7%..

Different Classifications of Adverse Drug Reactions:

- **Type A (Augmented)** Reactions: are those related to exaggerated pharmacological effects of drug & tend to be fairly common (usually more than 1 in 100)
- **Type B (Bizarre)** Reactions: are those that are unexpected & unpredictable, have genetic predisposition, allergy etc., are often serious.
- **Type C (Chronic)** Reactions: which are due to long term use of drug.
- **Type D (Delayed)** Reactions : e.g., teratogenesis, carcinogenesis.
- **Type E (End of Use)** Reactions: which occur when discontinuation of drug is too abrupt
- **Type F:** Failure of therapy.

The main sources of ADR data are:

- (a) Spontaneous reporting by doctors, Pharmacists nurses etc;
- (b) ADR monitoring schemes in hospitals
- (c) Clinical trials (all phases including post marketing surveillance)
- (d) Vital statistics (mortality, morbidity registers, birth registers for congenital defects)
- (e) Special studies (case control studies, cohort studies)

SEVERITY OF ADR'S:-

- **Mild.** ADR considered to be mild when it does not need any treatment viz., sedation with antihistamines.
- **Moderate.** ADR considered moderate when there is a need to change drug or leads prolonged stay in hospital.
- **Severe.** Potentially life-threatening, needs shifting to hospital / ICU or leads permanent damage.

Serious Adverse Event

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death:-

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening:-

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged):-

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required

intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage:-

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect:- Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child¹⁶⁻¹⁷.

6. CLASSIFYING ADVERSE EVENTS

Adequate review, assessment, and monitoring of adverse events require that they be classified as to **severity**, **expectedness**, and potential **relatedness** to the study intervention. Study protocols must include a description of how adverse events will be classified in these terms. These classifications determine the reporting requirements.

Severity:-

Classifications often include the following:

Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Severity is not synonymous with seriousness. A *severe* rash is not likely to be an *SAE*. Likewise, a *severe* headache is not necessarily an *SAE*. However, *mild* chest pain may result in a day's hospitalization and thus is an *SAE*.

Expectedness:-

AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label. Categories are:

Unexpected - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

Expected - event is known to be associated with the intervention or condition under study.

Relatedness

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

Definitely Related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

Not Related : The adverse event is clearly not related to the investigational agent/procedure. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Reporting Adverse Event:-

REPORTING PROCESSES:

Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Problems have specific reporting procedures.

Adverse Event Reporting:-

All AEs are collected on an Adverse Event Form, a sample of which is shown in Adverse Event Form AEs and/or laboratory abnormalities must be reported. All AEs experienced by the participant during the time frame specified in the protocol (e.g., from the time study drug administration through the end of the study) are to be reported, as outlined in the protocol.

Please note that the AE form contains a column to indicate whether the event is SERIOUS. Thus, SAEs are a subset of the reported AEs.

Routine reporting of AEs is described in the DSMP and may be monthly or quarterly as determined with the NIA staff and / or the DSMB/Safety Officer.

Serious Adverse Event Reporting:-

All SAEs, unless otherwise specified in the protocol and approved by the IRB and NIA or DSMB (as applicable), require expedited reporting by the Principal Investigator to the study's safety monitoring bodies. An expedited report of an SAE can be submitted by telephone, fax, or email and must be reported to the independent safety monitoring body (i.e., DSMB or Safety Officer) and the NIA within 24 hours of the event being reported to the Investigator or as specified in the DSMP.

The expedited report should be followed by detailed, written SAE report as soon as possible. Follow up information may be required and asked for by the independent safety monitoring body directly, or through the NIA or its representative. A sample of the SAE reporting form used for NIH Intramural Programs is shown in Serious Adverse event Form¹⁶.

Unanticipated Problems (UP):-

Investigator institutions must have written procedures for ensuring prompt reporting to the IRB and NIA, and others as appropriate, of any Unanticipated Problem involving risks to study participants or others (45 CFR 46.103(b)(5)). The Unanticipated Problems reporting procedures must include a corrective plan and measures to prevent reoccurrence. It is recommended that such events be reported within 48 hours to NIA unless they are also SAEs.

Components of a case report:-

- **Identifiable Patient:** At least one of the details should be available (Age, DOB, sex, history, case identification i.e Patient ID)
- **Product:** Clearly refers to name of a drug or biologics or any device
- **Adverse event:** (Sign, symptom, severity, diagnosis, outcome, Action taken, dechallenge, rechallenge, Laboratory data,, drug exposure (Dose, dosage, concomitants, Indication, overdose, misuse)
- **Source:** Identifiable reporter (Consumer/Patient, Legal source)

Methods in Pharmacovigilance/types of reports :-

- Spontaneous Reporting: AE report from any unsolicited source (Legal)
- Clinical studies
- Prescription Event Monitoring (Solicited reports)
- Literature reports
- Registry reports
- Case Control Surveillance
- Record Linkage (automated population databases; 'data mining')
- Medical device complains¹⁷⁻¹⁸

Case Study of Patient Pratigya Choudhary

| S.No. | Name | Findings |
|-------|---------------------|--|
| 1 | Name | Ms. Pratigya Choudhary |
| 2 | Age | Four and Half Years old |
| 3 | Sex | Female |
| 4 | History | Patient was feeling pain stomach and Drugs given Amoxicillin and potassium clavulanate combination and paracetamol syrup after two dosage eyes and urine were dark yellow. |
| 5 | Case Identification | Clinical Laboratory tests performed |

| | | |
|---|--------------------|--|
| 6 | Adverse Event | |
| | a. Sign | Dark Yellow Eyes and Urine |
| | b. Symptoms | Jaundice Confirm |
| | c. Diagnosis | Jaundice |
| | d. Outcome | Patient was serious |
| | e. Laboratory Data | Confirm the Jaundice |
| 7 | Source | Health care professional (Symptoms and Clinical Laboratory data) |

7. CONCLUSION

This study has completed in preparing report of Pharmacovigilance and Adverse Drugs Reaction. A case study is done on patient suffering from Jaundice after gating dose of Amoxicillin and potassium clavulanate combination and paracetamol syrup. The report was send to the National Coordinate Centre IPC, Ghaziabad, India.

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