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SAFETY DATA GENERATION IN GUIDANCE OF GOOD CLINICAL PRACTICE BY INTERNATIONAL COUNCIL FOR HARMONISATION (ICH) GUIDELINES

Komal Singh*, Sunil Kumar and Umesh Kumar Sharma

Department of Pharmaceutical Sciences, Nandini Nagar Mahavidyalaya College of Pharmacy, Nawabganj Gonda-271303 U.P. India.

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***Corresponding Author**
Komal Singh
Department of Pharmaceutical Sciences, Nandini Nagar Mahavidyalaya College of Pharmacy, Nawabganj Gonda-271303 U.P. India.

ABSTRACT

There has been an increased prominence on the proactive and extensive evaluation of safety endpoints to ensure patient well-being throughout the medical product life cycle. In fact, depending on the severity of the prime disease, it is important to plan for an extensive safety evaluation at the start of any development program. Statisticians should be informally involved in this process and contribute their prowess to study design, safety data collection, analysis, reporting (including data visualization), and elucidation.

KEYWORDS: Adverse events, clinical trials, safety monitoring, GLP, life intimidating etc.

INTRODUCTION

Modern drug safety and pharmacovigilance launched into in the preliminary 1960s following the thalidomide disaster. Thalidomide, a drug sketched to avert morning sickness, was released in 1959 and evolved in over 10,000 children in 46 countries being born with birth defects. In the rouse of thalidomide, the World Health Organization (WHO) established the Programme for International Drug Monitoring (PIDM). Today, PIDM has greater than 150 participating countries, with over 16 million Adverse Event Reports (ADRs) assembled. In parallel, the United States Congress precedes the Kefauver-Harris Drug Amendments (1962). For the first time, these laws prerequisite drug makers to demonstrate their drugs worked safely before the Food and Drug Administration (FDA) would authorize them for sale. These

changes were the start of a sign of regulatory changes sketched to secure reliable evidence of drug safety, efficacy and chemical clarity prior to market release. While a lack of clinical efficacy is the considerable cause of drug attrition, a poor safety profile is also a significant factor in the negligence of drugs during development. This may happen at any stage in the development process, from beginning drug discovery to preclinical trials, clinical trials and post-marketing surveillance (Pharmacovigilance).

The medicinal product's safety and efficacy should be demonstrated by clinical trials which follow the guidance in 'Good Clinical practice: Consolidated guidelines' (ICH E6) adopted by the ICH (international conference of harmonization) 1May 1996. The statistic's role in clinical trial design and analysis is acknowledged as essential in that ICH guidelines. The statistical research's proliferation in clinical trial's area coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on the statistical issues related to Clinical trials by Nirali Prakashan. Clinical trials provide the affording evidence basis for regulatory approvals of safe and effective medicines. With long development cycles and ever-increasing costs in conducting clinical trials, both the pharmaceutical industry and regulators are to do something to be more proactive in safety evaluations. Early safety signal detection detected both the better patient protection and the potential to save development costs. Since clinical trials experiment are in humans, they must be conducted that established standards in that order which protect the rights, safety and well-being of the participants. These standards contain the International Conference of Harmonization Good Clinical Practice (ICH-GCP) guidelines.

The Clinical trials globalization has presented additional challenges to the sponsors. The sponsors are held accountable to comply with contingent local legal and regulatory requirements wherever the clinical trials are accompanied. For example, clinical trial accompanied in the European Union are required to be accompanied in accordance with the Clinical Trials Directives. Central Component that is safety evaluation in all stages of drug development lifecycle. Proceeding to the marketing legitimatization of drug, meticulous safety monitoring and evaluations from preclinical to all stages of clinical trials are required. Pharmaceutical sponsors need to competently characterize the safety profile of the product in order to obtain consistently approval and marketing legitimatization. The authorized product label contains the prerequisite information about the product's benefits and risks. The continued vigilance in safety is condemnatory more data and experience is assembled from a

wider patient population once the product is on the market. In some cases, new appearing safety profiles may cast the original benefit-risk judgements in doubt. These are revealed in some High profile market withdrawals, such as Troglitazone (Rezulin), Rofecoxib (Vioxx) and Rosiglitazone (Avandia). In 2005, the United States Food and Drug Administration (FDA) issued guidance documents on risk management activities, Including premarket risk judgement and post marketing pharmacovigilance and Pharmacoepidemiologic judgments of project.

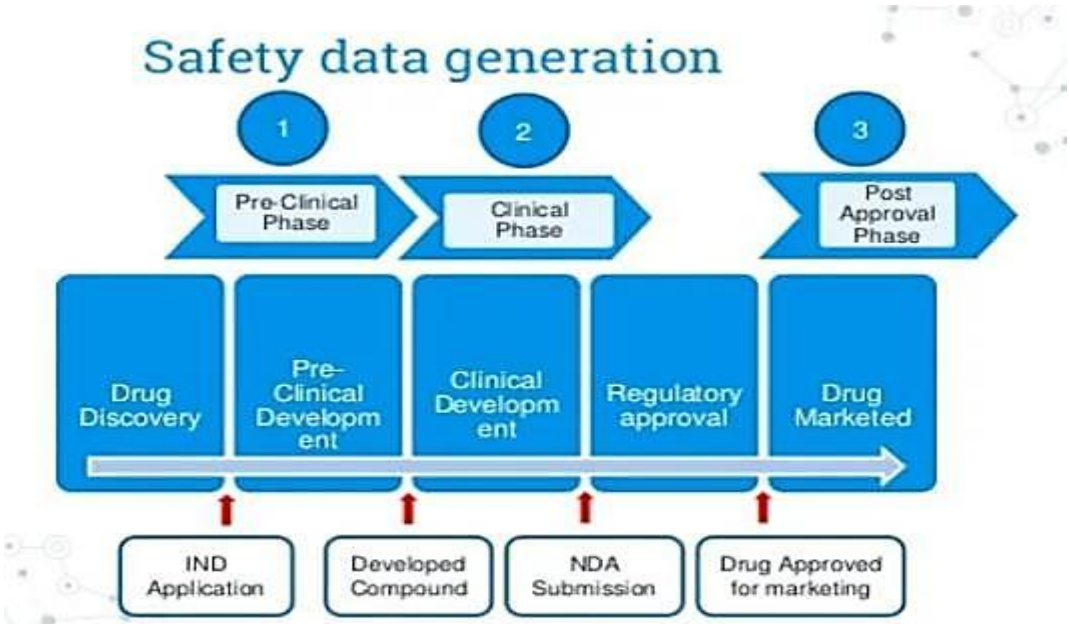


Figure No.1: Safety Data Generation At Different Phases.

Source: https://www.slideshare.net/ramesh_2417/safety-data-generation.

ICH E10 and M3 guidelines

E1A:- The Population Extent Exposure to Asses to Clinical Safety.

E2A:- Clinical Safety Data Management: Definition and Standards for Accelerated Reporting

E2B:- Clinical Safety Data Management: Data Elements for Transference of Individual Case Reporting.

E2C:- Clinical Safety Data Management: Periodic Safety Update Report for Merchandise drugs.

E3:- Clinical Study Report's contents and structure

E4:- Dose – Response details to Support Drug Registration

E4:-Ethnic Factors in the Applicability of Foreign Clinical Data

E5:-Consolidated Guideline of Good Clinical Practice

E7:-Considered in Support of Special Population: Geriatric

E8:-General Deliberation for Clinical Trials

E10:- Alternative of Control Group in Clinical Trials

M1:- Harmonization of Medical Terminology for Regulatory Purpose.

M3:- Non-Clinical Safety Studies for the managing of Human Clinical Trials for Pharmaceutical.

Drugs withdrawn for safety reasons

Drugs	Reason for withdrawal
Practalol	Oculomcocutaneous reaction
Troglitazone	Liver damage
Cerivastatin	Skeletal muscle damage
Rofecoxib	Myocardial infarction
Furazolidine	Cancer
Analgin	Bone marrow depression

Figure no 2: drugs withdrawn for safety reasons.

Source: https://www.slideshare.net/ramesh_2417/safety-data-generation

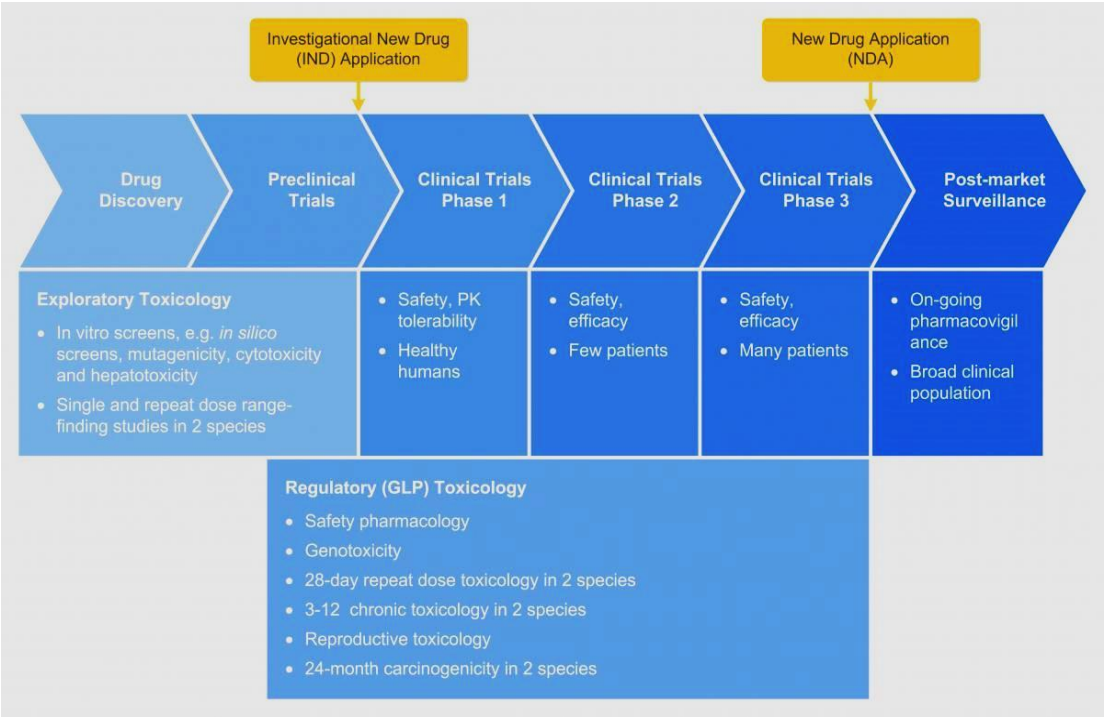


Figure no.3 timing of main safety assessment studies.

Source: https://www.linguamatics.com/solutions/drug-development-safety-and-pharmacovigilance.

Drug Discovery

Typically this involved highly parallelized processes for making new compounds and testing them in high-throughput screens. From this, a certain number of hits will be obtained and these will be whittled down by further analysis into a set of leads.

Pre-clinical Trials

This includes in vitro and in silico testing of the compounds to identify the best members of a series to take into Clinical Trials. This is also where the first stages of safety assessment are undertaken via toxicity testing in animals. If a drug shows promise in preclinical trials, a pharmaceutical company can request permission from the FDA to begin testing in humans (known as First-in-Man or FIM trials). This is called an Investigational New Drug (IND) application. In Europe, the European Medicines Agency (EMA) equivalent is an Investigational Medicinal Product Dossier (IMPD).

Phase -1Clinical Trials

Phase 1 clinical trials are perturbed primarily with demonstrating how a drug is absorbed, distributed, metabolized and excreted by the human body – a study known as pharmacokinetics (PK). The dosage range of a new drug is prompted by administering increasingly larger doses to one or more groups of subjects, who are closely observed for harmful side effects. The goal is to the assimilate maximum tolerated dose that does not produce unacceptable side effects.

Phase-2Clinical Trials

Subjects in a phase 2 clinical trial may satisfaction from their involvement if they encounter an active treatment. Most phase 2 clinical studies are scrambled, with subjects designated randomly (by chance and not by choice) to collect the experimental drug, a standard treatment or placebo (harmless, inactive substance). Since larger numbers of patients collect a treatment in Phase 2 clinical trials, there is a greater prospect to perceive and compile information on potential side effects.

Phase-3 Clinical Trials

Phase 3 clinical trials are managed at multiple centers with hundreds or thousands of patients for whom the drug is deliberated. Testing on wide-ranging patient populations permits continuous generation of data on a drug's safety and efficacy. As in phase 2, most phase 3 clinical trials are recombined and intimidated. A drug in this phase can be considered for several years.

New drug application (NDA)

Once the Phase 3 clinical trials are finish, a pharmaceutical company can appeal FDA approval to market the drug within the USA. This is called a New Drug Application (NDA). The NDA hold all the scientific data that the company has accumulated during clinical trials. Within the EU, pharmaceutical companies yield a Marketing Authorization Application (MAA).

Regulatory (GLP) Toxicology

These studies are executed to Good Laboratory Practice (GLP) standards and contain those required by local regulatory authorities or ethics committees prior to a drug can be given to human subjects for the first time. Regulatory toxicology also balance the learn required to support a New Drug Application (NDA).

Post marketing surveillance

Overseen by the FDA or EMA, post-market surveillance is planed to secure the safety of a drug once it announced onto the market. Pharmacovigilance is planed to secure that regulators monitor any adverse events described by the public who may be tolerating from a wide range of medical conditions (far wider than those to which the drug would have been exposed during clinical trials).

Pre-Clinical Phase Development

- In-vivo and in-vitro studies
- **Exploratory toxicology :** these study provide a irregular quantitative estimate of toxicity of the compound when given extremely and frequently over a short period. It provides an manifestation of the main organs and physiological system involved.
- **Regulatory toxicology**: These studies are executed to GLP standards and understanding those that are required by Regulatory authorities. Also execute to support an application for marketing approval.

EXPLORATORY TOXICOLOGY

In-vivo and in-vitro screening for:

- Mutagenicity
- Cytotoxicity
- Immunotoxicity
- Hepatotoxicity
- Embryotoxicity
- In- silico screening

REGULATORY TOXICOLOGY

- Safety pharmacology
- In-vitro and in-vivo studies
- GLP guidelines
- 28 days repeat dose toxicity and recovery in 12 species
- 3-12 months chronic toxicity in species
- Reproductive toxicity in 1 species

SAFETY PHARMACOLOGY

- Core battery of tests
- Follow up tests
- Supplementary tests

Core battery of tests

System	Tests
CNS	Motor activity Behavioral changes Body temperature Coordination
CVS	Blood pressure Heart rate ECG changes
Respiratory system	Respiratory rates Tidal volume

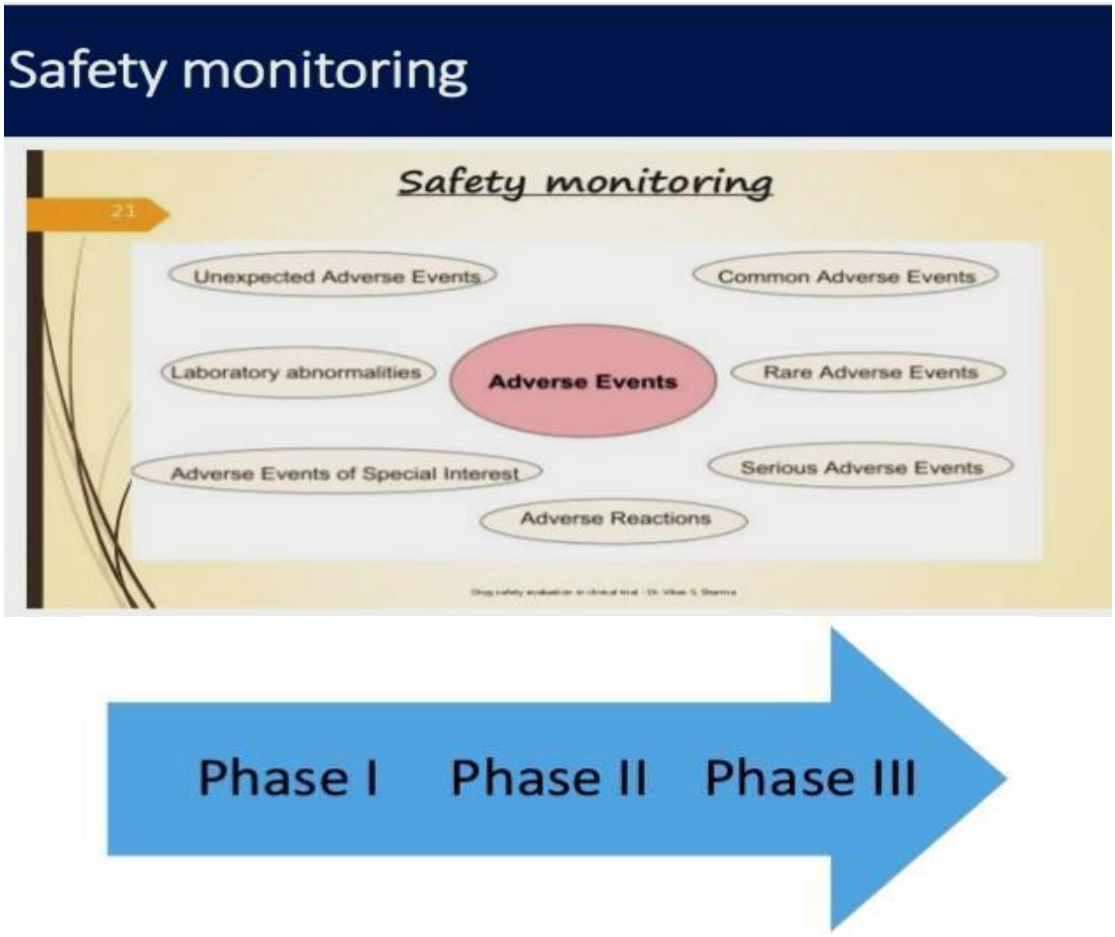
Follow-up tests

System	Tests
CNS	Tests on learning and memory Tests for motor function Tests for visual function
CVS	Cardiac output Ventricular contractility Vascular resistance Regional blood flow
Respiratory system	Airways resistance Pulmonary arterial pressure Blood gases

Supplementary tests

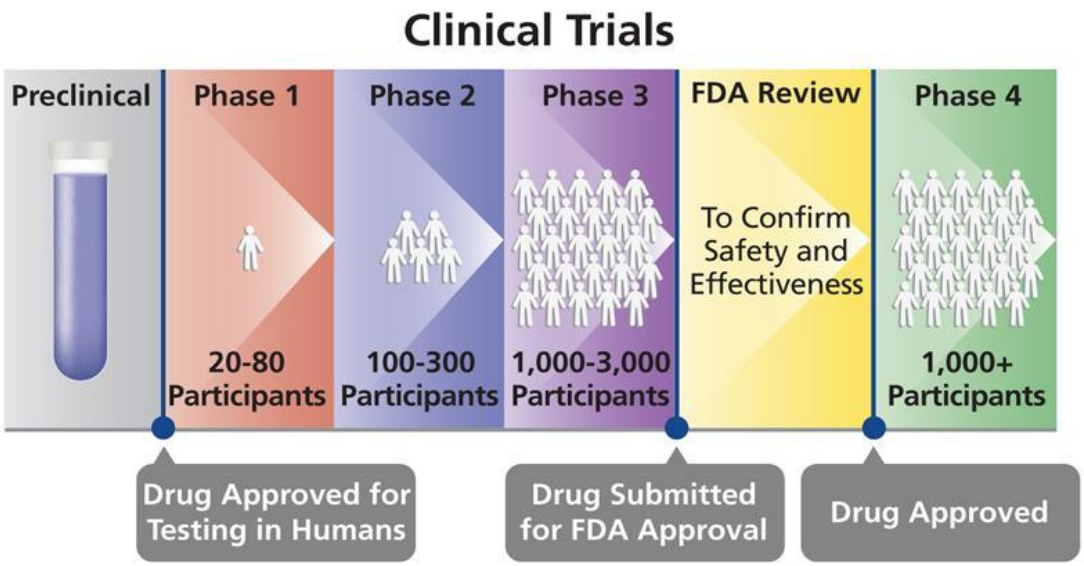
System	Tests
Renal function	Urine volume, pH Proteinurea Blood urea, creatinine
ANS	CVS, GIT and respiratory responses to agonists, stimulation of autonomic nerves
GIT	Gastric secretion, pH GI motility, GI transit time

Source:https://www.glocaluniversity.edu.in/files/eContent/eBpharm/SKS%20preclinical%20safety%20data%20generation.pdf

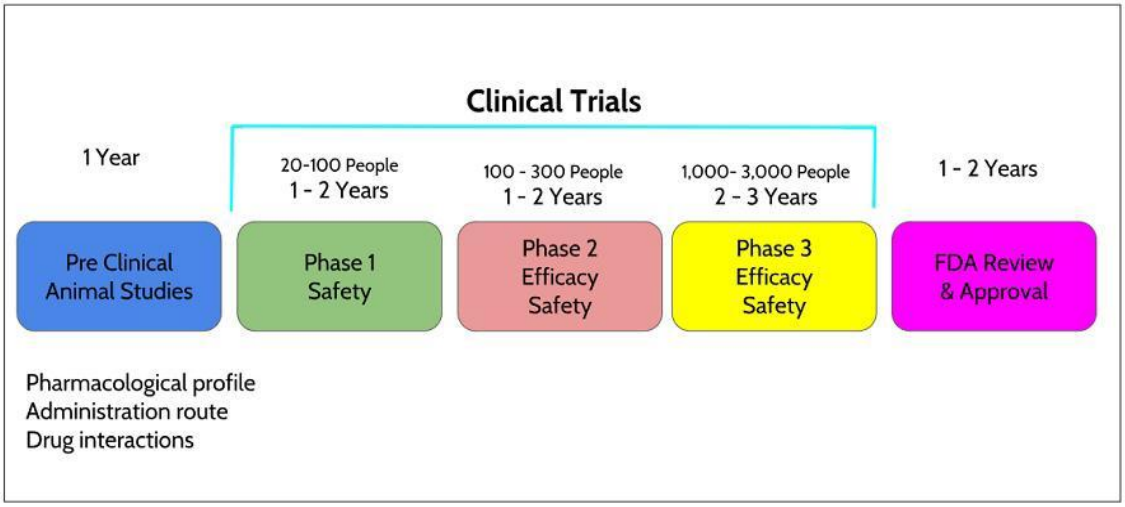


SAFETY DATA IN CLINICAL TRIALS

Source:https://www.slideshare.net/dr31sharma/drug-safety-evaluation-in-clinical-trial Source.



Source:- https://onlinesciencenotes.com/different-phases-of-clinical-trials-drugs-testing-and-development-of-vaccines-in-clinical-research/



Source:- https://www.jliedu.com/blog/clinical-trial-phases/

Adverse Event

- Any unexpected medical occurrence discerned during treatment with pharmaceutical product which does not automatically have a causal relationship with the treatment.
- Any advanced clinical experience
- Adverse consequence that occurs after use of a drug
- May or may not be associated to the use of a drug
- Examples: cardiac arrhythmia after desist atenolol, abnormal ECG report, abnormal lab report.

Sources of safety intelligence and assessment

- Unconstrained ADR reporting schemes
- Data from clinical and epizootiological studies
- Data from pharmaceutical companies
- Journals data source
- News headlines
- Data accessible with regulatory authorities
- Safety description of other drugs of similar class/type
- Data from pre-clinical studies

Serious Adverse effect

- Any unexpected medical phenomenon that at any dose results in death
- Life intimidating
- Requires inpatient ministrations
- Decompensation of existing ministrations
- Results in tenacious or significant affliction
- Results in inherited birth defect
- Requires interpose to prevent permanent

Unpredicted Adverse Event

- The nature or extremity of which is not compatible with the applicable product intelligence
- Not compatible with the risk information described in general investigational plan of investigation prospectus
- Not listed at the heterogeneity or extremity observed
- Not listed in investigator's prospectus

Experimental new drug safety reporting requirement

- Any unpredicted or life intimidating adverse events must be reported more rapidly to FDA
- Any unpredicted or life intimidating adverse events must be reported within 7 days
- A major safety uncovering from a newly completed animal study such as carcinogenicity
- A remarkable hazard to the patient population such as lack of efficacy with a medicinal product used in treating life intimidating diseases.

Adverse event reporting time line

- Death and life intimidating-serious adverse events must be reported must be reported by the sponsor to the regularly authority within 7 days
- Any other unpredicted AEs that are neither fatal nor life intimidating should be reported within 15 days

Post marketing safety

- Post marketing monitoring
- Clinical trials are managed for a limited period
- Small number of contributors are involved in clinical trials
- No real life setting in clinical trials
- PMS can refine, confirm or contradict the safety of the drugs

Post marketing safety

- Approach to monitor the safety licensed drugs
- Spontaneous reporting database
- Prescription event monitoring
- Electronic health records
- Patient registries
- Observational studies
- Product's pre approval safety profile
- Current FDA- approved leve

Post marketing Reports

- Repeated safety update reports
- PSUR process
- Expenditure of ADR information
- Data sort out
- Data inspection
- In India PSURs should be yield every 6 months for first two years and annually for consecutive 2 years.

Post marketing reports

- For secure safety on long term and on a larger population

- Regularly authorities ask the marketing authorization holders (MAH) for reporting of AEs and agreement of periodic safety reports.
- For serious and unexpected AEs, FDA recommends reports to be submitted within15 days.
- Follow up to 15 day alert reports should be tender within 15 days.

RESULT

We share our exhortation for the statistical methodology necessary to suitable analyze, report and interpret Safety outcomes, and we discuss the advantage and disadvantage of safety data obtained from Clinical trials compare to other sources. In the document, we review the challenges associated with the analysis of safety endpoint and narrate the safety data that are available to influence the design and analysis of premarket clinical trial.

CONCLUSION

Clinical trials are an important spring of safety data that impart to the totality of safety information accessible to generate corroboration for regulators, sponsors payer, physician and patients. This work is result of a venture of the American Statistical Association Biopharmaceutical Section Safety Working group.

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