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ACCELERATING OUTCOMES

Signal Detection in Early Phase Clinical Drug Trials

WHY SHOULD YOU PERFORM SIGNAL DETECTION IN EARLY PHASE CLINICAL DRUG TRIALS?

The term ‘pharmacovigilance’ has conventionally been related with post-marketing activities; however, it is also equally applicable to the pre-marketing process for collecting, managing & assessing safety information during clinical development of the molecule. Similarly, the concepts of signal detection and assessment, risk assessment and risk minimization are as applicable to the pre-marketing scenario as they are to the post-marketing scenario.

The importance of this is evident from the following examples:

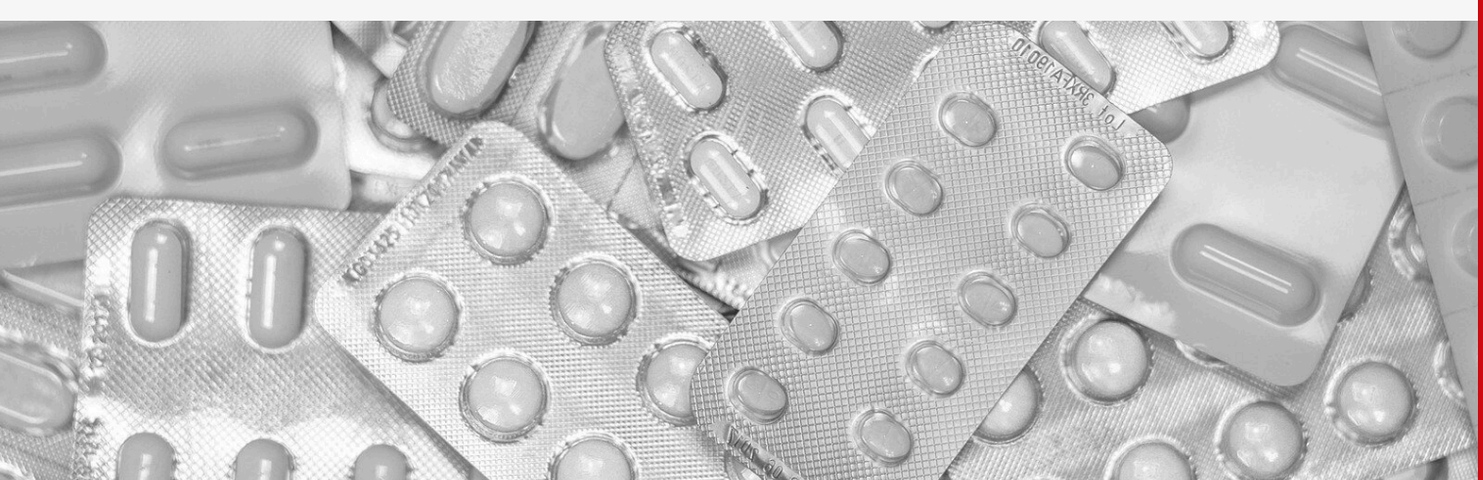
Drugs Not Approved in USA

Examples of drugs not approved in USA as premarketing experience provided evidence of the potential for severe DILI e.g., dilevalol, tasosartan, ximelagatran.

Drugs withdrawn from market worldwide after initial regulatory approval

E.g., rimonabant, rofecoxib, celecoxib etc.

The safety information generated at the end of clinical development program should be extensive enough to permit comprehensive regulatory review and determination of benefit-risk profile for supporting marketing approval. The information should be comprehensive so that product label can be adequate to provide prescribers & patients adequate information for safe use of the drug.



WHAT DO THE REGULATORS SAY?

USFDA 21CFR312.32
USFDA Draft Guidance on Sponsor Responsibilities June 2021

Sponsors must adopt a systematic approach to safety surveillance to meet IND safety reporting requirements and enhance quality of safety reporting.

Such an approach involves promptly reviewing, evaluating, and managing safety information from all sources, including animal studies, clinical investigations, scientific literature, professional meetings, foreign regulatory authorities, and commercial marketing experience.

USFDA 21CFR312.56
USFDA Draft Guidance on Sponsor Responsibilities June 2021

The sponsor's review should involve assessing data from all sources and monitoring the progress of investigations:

- To identify previously undetected potential serious risks (§312.56(a)).
- To update investigator's brochure, protocol, and consent forms with new information.
- As necessary, to take measures for protecting subjects (e.g. monitoring, modifying dosing, or participant selection) (§312.56(d)).

CIOMS Working Group VI

The purpose of ongoing safety evaluation during drug development is to ensure that important safety signals are detected early and to have a better understanding of benefit-risk profile of study drug.

Sponsors should develop a system to analyze, evaluate and take actions on the safety information on a continuous basis. This is to ensure the earliest possible detection of safety concerns and allow suitable risk minimization.

Systemic Approach for Signal Detection

Early Phase (I/II) CTs

- Smaller patient numbers, safety profile relatively unknown
- Frequent review – fortnightly/monthly with signalling report every 15 days/monthly
- Manual review of adverse events (AEs), laboratory data, and vital signs
- Intensive monitoring for DLTs and AESIs
- Special Monitoring (as needed) : E.g. Utilization of eDISH plots for detecting drug-induced liver injury

Late Phase (Phase III)

- Larger patient numbers
- Can perform manual review; helpful if there is a robust signalling process in place to ensure the timely availability of safety data in the right format
- Large datasets may need statistical review / Use of Software to review external datasets for class effects etc./Statistical tools for analysis of Aggregate Review

Periodicity of Review

- Routine, periodic, general review of safety data
- Ad hoc for serious and special interest AEs
- Reviews triggered by specific milestones in a trial or a program (e.g., no. of completed patients, end-of-trial, end-of-program, Aggregate Reports, preparation of integrated summary of safety)

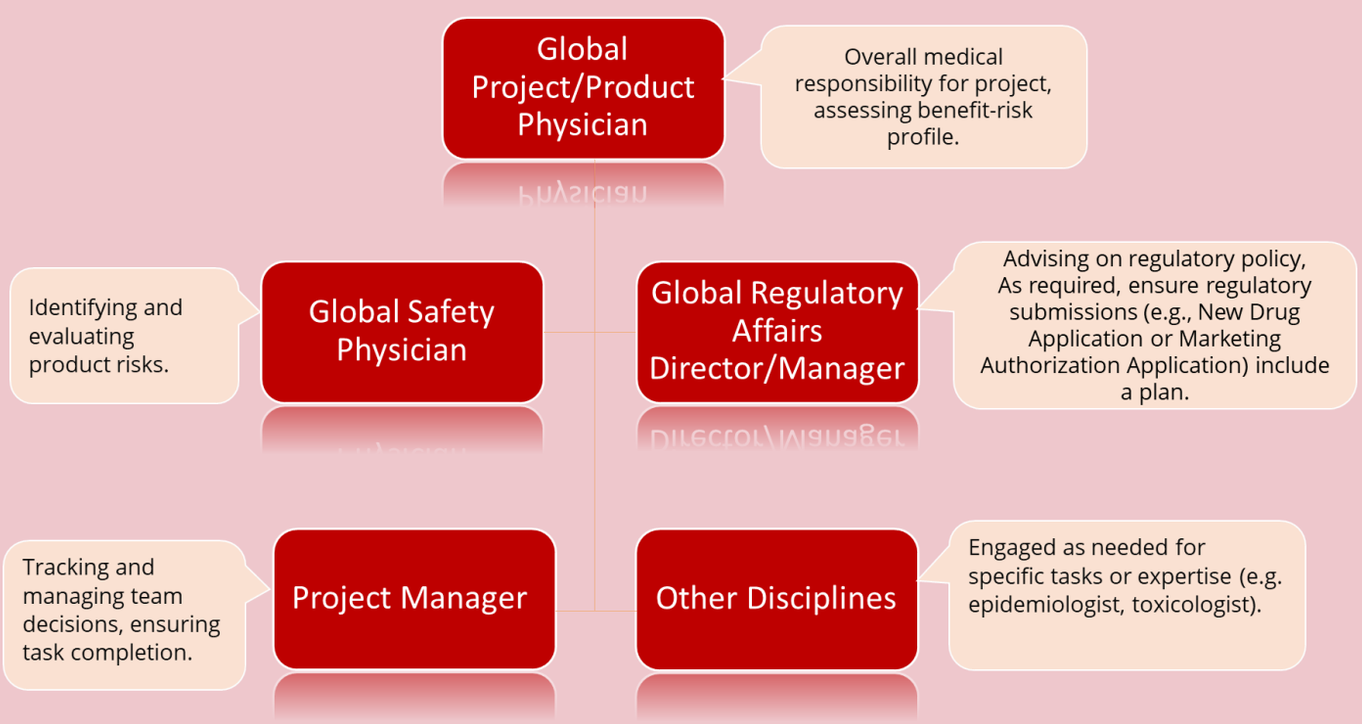
Essential Elements for Effective Signal Detection in a Clinical Development Program

- ✓ Early Initiation is Crucial
- ✓ Written Process Required for Review
- ✓ Multidisciplinary Safety Management Team (SMT)
- ✓ Data from Licensing Partners to be Considered
- ✓ Project Management Function
- ✓ Background Incidence
- ✓ Ready Data Accessibility
- ✓ Initiative Proactive Strategy
- ✓ Establish Timeframes and Milestones
- ✓ Decision Making
- ✓ Advisory Bodies

Signal Detection: Effective Data Review

Below are some of the key points that support effective data review during signal detection process in a clinical development program:

Parameters	Overview
Analyze all AEs - Serious and Non-serious	The safety analysis is complete when all adverse events (serious and non-serious) are reviewed, with a greater emphasis on those leading to treatment discontinuation.
Review of Individual Cases	Individual case is an essential unit of safety analysis. SARs and AESIs are a vital source that can suggest a safety signal. Patient population, drug indication, and natural history of disease should be considered during analysis.
Aggregate Review of Safety Data	Aggregate review is essential to analyse evolving safety information. Interval and cumulative data are assessed simultaneously. Attempts should be made to analyse data per various dose /cohort, duration, gender, age etc.
Review of Clinical Lab Data	Laboratory tests are useful for screening subjects, early detection of organ toxicity & detection of potential toxic effects. Special focus should be on lab values correlating with organ toxicity e.g., endocrine abnormalities, hepatotoxicity etc.
Adverse Events of Special Interest (AESI)	The protocol should define AESIs emphasizing the need for clear identification, close monitoring, and prompt reporting. Examples – Prodromal events suggesting rhabdomyolysis, events impacting quality of life such as hair loss etc.



Structure of Safety Management Team

Development Risk Management Plan (DRMP)

A Development Risk Management Plan (DRMP) is a natural extension of high quality pharmacovigilance. In DRMP, a compound-specific approach should be adopted, possibly as part of the broader Clinical Development Plan. It should contain early documentation of identified, expected, or potential risks, along with strategies for addressing them throughout development. As appropriate, the DRMP may develop into a post-marketing risk management plan.

The DRMP is a guide for safety surveillance during development and is not a legal or regulatory document; however, the following two actions must be considered during development of the process:

1. Recognize the potential for legal discovery of DRMP and ensure appropriate language clarifying its status as a working document.
2. Establish robust processes, including project management to ensure the diligent execution of the action plans.

The DRMP should include the following sections: anticipated product profile, epidemiology, non-clinical safety experience, clinical safety experience, identification and assessment of known or anticipated risks, identification and assessment of potential new risk, and actions and/or plans for evaluating and mitigating risk.

Conclusion

The concepts of signal assessment, risk assessment and risk minimization are as applicable to pre-marketing scenario as they are to the post-marketing scenario. The purpose of ongoing safety evaluation is to ensure that safety signals are detected early and to obtain an understanding of benefit-risk profile of the drug. Signal detection during clinical trials is usually performed based on clinical judgement, since there is limited data available during premarketing clinical trials. The three basic attributes for signal detection includes quick medical assessment, periodic aggregate assessment, and safety evaluation of completed unblinded trials. To ensure effective signal management, it is important to establish an effective system, beginning early, having proactive approach, analysing all serious and non-serious events, periodic reviews by scientific committees, and prompt decision making.

References

1.Report of CIOMS Working Group VI: Management of Safety Information from Clinical Trials: Geneva 2005.

2.Report of CIOMS Working Group VIII: Practical Aspects of Signal Detection in Pharmacovigilance: Geneva 2010.

3.USFDA Guidance for Industry: Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies: June 2021.

4.21CFR312.32: Subpart B - Investigational New Drug Application (IND): IND safety reporting.

5.21CFR312.56: Subpart D - Responsibilities of Sponsors and Investigators: Review of ongoing investigations.

6.European Medicines Agency: Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1); Dated 22 November 2017.

About Authors

Dr. Sumit Verma MD, DNB - President, Clinical Safety & PV

Dr. Sumit Verma is a medical graduate with specialization in anesthesiology and has more than 15 years of experience in the pharmaceutical industry, clinical medicine, clinical research, and pharmacovigilance. He has built teams that have consistently delivered and exceeded customer expectations across pharmacovigilance domains such as case processing, signal management, risk management, aggregate reports, and clinical safety. He has co-authored two books – one on pharmacovigilance and another on pharmacology.

Dr. Yogesh Gulati MD - Sr. Safety Physician, Clinical Safety & PV

Dr. Yogesh Gulati is a medical graduate with specialization in pharmacology and has more than 13 years of experience in the pharmaceutical industry, clinical research, and various phases of clinical trials. He has led various pharmacovigilance teams comprising of physicians and clinical research coordinators in conducting pharmacovigilance activities for various global clients. He has been involved in setup of a standalone pharmacovigilance unit and gradual scale up of operations while ensuring system and regulatory compliance. He has managed teams producing high-quality documents in pharmacovigilance domains, including case processing, signal management, risk management, and aggregate reports, and co-authored books on pharmacology and nursing drug guide.

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About Soterius

Soterius is a strong team of pharma professionals who design customized, innovative, and cost-efficient processes for clinical safety, pharmacovigilance, and medical affairs. Our deep industry knowledge and up to date insights let us combine agile, people powered intelligence in pioneering customer centric solutions. Our innovative technology solutions include engagement tools and communications platforms to create a unified and compliant medical access facility. With a strong global presence, we provide comprehensive clinical and post marketed safety services, that include aggregate report writing, signal detection and management, global literature surveillance, risk management, case processing and regulatory reporting.

We use state-of-the-art technologies to solve complex safety operations problems, be it case processing, intake, site reporting for clinical trials, or literature search and management. We have one of the most accurate solutions for case intake and case processing using AI.

We support companies from the initial development stage of a drug/vaccine to the approval and ultimate marketing of the therapy, supporting ongoing operations and regulatory commitments globally.

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