FINDING THE SUBTLE SAFETY SIGNAL

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Abstract

Objective: Safety issues are critical in the development of novel therapeutics. Complicating the development process are multiple trials in different geographies, inconsistent data treatment, multiple sponsors, CROs, and poor database design including variations in reporting. As the pace of development increases and global development programs become norm, finding the safety signal becomes more challenging yet, if accomplished, improves the efficiency and success of the drug development process.

Methods: Although safety is monitored and evaluated during the clinical development phase, broad patient exposure often remains limited until after the successful commercial launch of the drug product. The withdrawal of promising therapeutics due to safety can also delay the introduction of needed therapeutics. Rigorous review of preclinical toxicologic, pharmacokinetic, and pharmacodynamic profiles, early clinical experience, and vigilant monitoring all contribute to finding subtle safety signals.

Results: Often data identifying safety signals exist, but are not noticed because of poor database design, or inadequate pooling (integration) of data. Data integration is an essential tool in safety evaluation. Assimilation of data across trials is potentially compromised for trials in different geographies, investigating different indications, and conducted by different sponsors or CROs. Complexity is introduced though multiple coding procedures and inconsistent treatment of data. Barriers to efficient data integration include variations in reporting concomitant medications and laboratory data.

Conclusions: Identifying safety signals can be optimized by combining information from preclinical research, integrating safety data across trials, and the consistent reporting and coding of information. Finding the subtle safety signal not only enhances the efficiency and success of the drug development process but is also a cost-effective project / resource management activity for the sponsor and minimizes risk.

Introduction

Although safety is monitored and evaluated during the clinical development phase, broad patient exposure often remains limited until after the successful commercial launch of the drug product. Successful data integration and rigorous review of preclinical toxicologic, pharmacokinetic, and pharmacodynamic profiles, early clinical experience, and vigilant monitoring all contribute to finding subtle safety signals.

Opportunities for improvement in the identification of safety issues exist during the following stages of a drug's life-cycle:

- Investigational drug development
- Market applications
- Post-marketing surveillance

The following figure illustrates how the safety profile expands and broadens during the major drug development phases.

The following safety challenges exist in the identification, reporting, and adjudication of adverse events and serious adverse events.

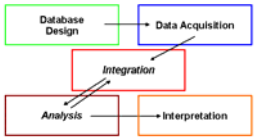
- Identification of unreported adverse events
- Timely reporting of serious adverse events
- Failure to report serious adverse events as SAEs when the adverse events are also efficacy parameters (e.g., death, myocardial infarction)
- Adjudication of adverse events from information collected:
  - SAE forms
  - Termination forms
  - Comment fields

Objective

Early identification of the safety signal to improve risk management, efficiency, and success of the drug development process.

Methods

A process needs to be developed to identify, integrate, and interpret the safety signals.



Results

Safety profiling is more rigorous during the pre-approval process compared to post-marketing surveillance.

Safety Profiling

	Pre-Approval	Post-Approval
Data Collection	Controlled	Spontaneous
Rate	Known	Unclear
Patient Population	Controlled	Uncontrolled

The patient populations in clinical trials (admission criteria) are expanded based on the risk-benefit assessment as a compound moves through development. Patient populations are modified during drug development as follows:

- Initially limited for risk assessment
- Defined to prove efficacy while limiting risk
- Expanded based on risk assessment
  - Phase I Normal volunteers
  - Phase II Proof of concept
  - Phase III Modeled on target market population

The pre-approval risk profile is often segregated into the following preclinical and clinical disciplines and technical assessments.

Preclinical	Clinical
Safety Pharmacology	Tolerability
Pharmacokinetics	Pharmacokinetics
Metabolism	Metabolism
Toxicology	Dose-Finding
Animal Models	Proof of Concept
	Dose Response
	Large Trials

However, a complete risk assessment is based on the integration of preclinical and clinical results.

Adding to the complexity, clinical data should be integrated, ideally, across the following:

- Trials conducted by more than one sponsor
- CROs
- Investigator INDs
- Legacy Databases

Aside from the adverse event form, adverse events can be identified from the following sources:

- SAE reports
- Indications for concomitant medications
- Termination forms
- Hospital discharge summaries
- Surgical reports
- Pathology reports
- Death certificates
- Comment fields

Integration of data across trials requires an evaluation of each trial to identify adverse events from the following sources:

- Adverse event forms
- Dictionaries
- Rx and OTC concomitant medications

Pooling of adverse events requires an assessment of the following trial information from the forms used, the database structure, and the data management decisions:

- AE Forms approach
  - One event - one form
  - At each visit
- Definitions of severity and causality
- Serious adverse events
- Database(s)
  - Adverse event only
  - Adverse event and SAE

Adverse Event Coding can be unified across a program as long as the following are addressed:

- Use of multiple adverse event dictionaries (e.g., COSTART, WHO, WHOART, MEDDRA)
- Inconsistent coding
- Inaccurate coding (misclassification of adverse events)

In the integration of laboratory data, the following must be addressed so that the data can be pooled:

- Different units
- Normal ranges
- Multiple central laboratories and local laboratories

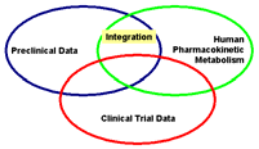
Pooling of data is required to detect trends of potential clinical importance early. This is particularly important in long-term blinded trials and individual trials with a small sample size.

Concomitant medication data integration also presents challenges:

- Coding: by drug class or indication
- Generic and brand names
  multiple names for the same drug
- Combination products
- OTC products
- Herbal products and other nutraceuticals

Conclusions

To detect a safety signal early, it is key to integrate the preclinical, pharmacokinetic, metabolism, and clinical trial data.



To optimize early detection of a safety signal, the following should be considered:

- Integration of preclinical and clinical assessments - *Comprehensive Integrated Safety Profiles*
- Periodic pooling of safety data across trials
- Third party safety review of ongoing trials
- Post-marketing surveillance exposure estimate

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