

Review Article

Role of Safety Evaluation in the Process of Drug Development: A Review

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ABSTRACT:

The role of drug safety guideline is to protect patients from occasional, severe adverse reactions; maximum efforts are directed at initial detection and preclusion of serious events. It is projected here that drug toxicity should be demarcated based not only on dose–response relationship, but also as a function of pharmacology, chemistry, metabolism, and environmental and genetic risk aspects. An effectual process can help us recognize safety signals early and give us the opportunity to develop efficient risk minimization plan initially in the development cycle. This alertness has led many pharmaceutical sponsors to arrange internal systems and structures to effectively carry out safety assessment at all levels. Furthermore, processing tools have appeared that are designed to improve data review and pattern recognition. Keeping patient safety during clinical trials under a check, is a perilous component throughout the drug development life-cycle. Pharmaceutical sponsors should work proactively and collaboratively with all stakeholders to safeguard a systematic approach to safety monitoring.

Key words: toxicology, serious adverse events, clinical trials, safety.

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INTRODUCTION

Emergence of 2019-nCoV (novel Coronavirus) has engrossed global attention recently, and World Health Organization has acknowledged COVID-19 as a public health emergency of international concern.¹Numerous attempts are being made to develop a drug to cure the infection by this novel virus. But to develop a pharmacologically active drug, is a daunting task and the sponsors/ companies who are trying to develop them quickly have to surpass minimum three stages of clinical trials so that market authorization of drug can be achieved which will mainly depend upon the number of adverse effects

associated with the intended drug and its risk to benefit ratio which is a lengthy procedure.

Toxicology Principles:

Traditional toxicologists trust on Paracelsus' Principle: "All things are poison and nothing is without poison. Exclusively the dose regulates that a thing is not a poison." This principle of toxicology found in the 15th century is the keystone of today's practice of toxicology. Dose–response relationship is the utmost vital data set from which safety is determined. For drugs, safety is projected based on the therapeutic index, a ratio of the toxic dose to the dose required for efficiency.² Safety assessment is a

fundamental component in all stages of the drug development lifecycle. Before marketing authorization of a drug, laborious safety monitoring and evaluations from preclinical to all stages of clinical trials are compulsory. Pharmaceutical sponsors need to sufficiently characterize the safety profile of the product in order to get regulatory approval and marketing authorization. The permitted product label contains the indispensable information about the product's benefits and risks. The constant vigilance in safety is critical as more data and knowledge is gathered from a broader patient population once the product is on the market.³

Drug Safety:

Clinical trials offer the evidentiary foundation for regulatory approvals of safe and effective medicines. Initial safety signal detection not only leads to improved patient protection, but also has the capacity to save development costs.⁴ Since clinical trials are experiments in humans, they must be directed following established standards in order to guard the rights, safety and well-being of the participants. These standards include the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines.⁵ The determination of the safety boundary, risk/benefit ratio analysis and investigation of adverse effects are major essentials for providing safety reassurance to patients. Safety of patients will also be enhanced through modelling methodologies permitting a safer switch of experimental pharmacology results to clinical pharmacology.⁶ To understand the safety assessment of a drug, one needs to consider the drug itself and its envisioned use. In addition to the drug itself, issues such as the dosing regimen, treatment duration and route of administration can affect the data vital to establish product safety.⁷ Numerous sources of information are used for drug safety e.g. spontaneous adverse drug reaction reporting schemes, clinical and epidemiological studies, worldwide published medical literature, pharmaceutical companies, international regulatory authorities and morbidity, mortality databases, nonclinical statistics, post marketing experience and safety profile of other drugs in the similar class. Information from all of these areas are carefully screened and may recognize unexpected side effects; representing that certain side effects occur more commonly than earlier believed, or that some patients are more susceptible to some effects than others.⁸

Pharmacovigilance:

Unexpected fatal or life-threatening suspected adverse reactions especially signify important safety information which consequently must be reported more rapidly to Federal Drug Administration (FDA). The prerequisite for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor's first

receipt of the information. If the safety report submitted within 7 calendar days is comprehensive, an extra submission within 15 days from day zero is not required.⁹ The role of drug safety regulation is to defend patients from rare, severe adverse reactions; most efforts are focused at early detection and prevention of serious events.¹⁰ Post-marketing surveillance through spontaneous adverse event reporting systems are the backbone of drug safety assessment.¹¹

DISCUSSION

Safety pharmacology is the main regulatory step for drug development and sanction.⁵ Developers of drugs, biologicals, and medical devices must guarantee product safety, validate medical benefit in people, and produce the product in great amount thereafter.¹² The product safety information accessible in a submission dossier for regulatory review which generally consists of non-clinical and clinical information.¹³ Species-variances in drug metabolism represent the prime reason for species-differences in turn in the drug toxicity. Pharmacokinetic drug-drug interactions, the consequence of one drug on the metabolic clearance of a co-administered drug, is also a chief mechanism of adverse drug effects.¹⁴ Timely review of this safety information is vital to ensuring the safety of study subjects. FDA supports a product when it judges that the benefits of using a product compensates the risks for the intended population and use. A major goal of the premarketing review is to safeguard that products are truthfully and adequately labelled for the population and use.¹⁵ The FDA White Paper identified the "Critical Path" as a process beginning with identification of a drug candidate and concluding in marketing approval. Along the path to marketing, the product is exposed to a series of evaluations to foresee its safety and effectiveness and to enable its mass production.¹⁶ Presently, preclinical safety testing includes traditional animal toxicology studies, as well as in vitro assays such as the Ames test. Animal toxicology tests are very valuable for evaluating safety for initial human testing; however, they frequently fail to uncover the types of toxicities seen after extensive human exposure. Novel technologies, such as gene expression assays in whole cell or animal systems, proteomics, or metabolomics, may offer much greater understanding into the whole spectrum of pharmacologic effects of a candidate drug. Drug developers are starting to use such technologies in the preclinical safety workup, and the clinical suggestions of such findings have not been worked out.¹⁷ Current proposals highlight the need to not just contemplate the magnitude and consequences of treatment effects, but also to assess fewer tangible factors such as the level of ambiguity and extent of risk tolerance. These developments are chiefly relevant when considering rare but serious adverse events where the clinical trials may harvest imprecise or even conflicting estimates. Multi-criteria decision

analytical techniques that precisely captures quantitative inputs and qualitative values from several stakeholders for risk-benefit trade-offs and permit for quantitative analysis and modelling uncertainty on a variety of outcomes can improve complex regulatory decisions about drug safety.¹⁸

CONCLUSION:

Current safety analyses during trials are critical in safeguarding that serious adverse events are discovered as soon as possible. Safety data from continuing clinical trials influence the clinical care of patients joined in those and other trials of a given drug; if the drug is by now in the market, these data may affect its clinical use.¹⁹ Safety reports resulting from ongoing clinical trials must be meaningful, relevant, and agreeable to timely analysis.

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