



Improving Critical Drug Development Decision Making Through Clinical Trial Simulation

Highlights:

- Incorrect selection of drug dose and schedule are leading causes of drug failure in clinical development.
- PK/PD Modeling enables drug exposure and drug response, together with an estimate of associated variability, to be predicted in the target patient population.
- It can also provide early insight on future dosing regimens, expediting protocol development, compressing development timelines, and helping to mitigate risk.

Introduction

The challenges in drug development are vast.

Why do many promising drugs fail in clinical development? The answer can be complex; however, a number of common problems have emerged in recent years together with mitigation strategies to minimize this costly risk of drug failure.

A recent article from the MIT Sloan School of Management published in the Journal Biostatistics has estimated the success rate of a product entering clinical development to be about 14%. Although this is higher than previous estimates, FDA approval rates can vary enormously depending on the therapeutic class, for example, from a high of 33.4% for vaccines and infectious diseases to as low as 3.4% for investigational cancer drugs. The cost of such failure can be enormous and potentially catastrophic for small/mid-size companies that are highly dependent upon new drug registrations to remain viable. So, what are the causes of this dismal record? Analysis of the principal causes of drug failure in the clinic reveals several weak spots including:

New technologies are aiding in the choice of dose and schedule before a clinical trial is even run.

- Incorrect selection of the drug dose and schedule
- Poor target validation and/or lack of biological activity
- Inappropriate choice of disease

Technology's Emerging Role in Clinical Trials

It can be argued that the most innovative and effective medicines will fail if the choice of dose and schedule is incorrect. Inappropriate dosing and scheduling can have dire consequences on both drug safety and efficacy resulting in late stage failure or registration delays while the problems are investigated and corrected. However, advanced PK modeling tools and computer-assisted trial simulation strategies can have a tremendous impact on how clinical trials are designed by providing a rational scientific basis for dose regimen selection, thereby mitigating these risks.

What is Clinical Trial Modeling and Simulation?

When we talk about modeling and simulation, what exactly do we mean? Modeling in this context can be regarded as a set of assumptions embedded in a mathematical equation that accounts for a series of pharmacological observations. Generally, drug action can be described by the union of pharmacokinetics (PK) (i.e. drug absorption, distribution, metabolism, elimination) with pharmacodynamics (PD) (i.e. the safety or efficacy characteristics of a given drug). PK/PD modeling unites these two processes to mathematically describe the link between drug exposure and drug response.

PK/PD modeling is not a new science; however, in recent years it has been significantly advanced by the development of population PK/PD and Monte Carlo-based simulation programs that can be used to design and simulate clinical trials. This approach is a powerful extension of classical PK/PD modeling as it integrates an established PK/PD model with estimates of variability. This enables drug exposure and drug response, together with an estimate of the associated variability, to be predicted in the target patient population. Perhaps the unique strength of this approach is the ability to run "what-if" scenarios on previously untested dosing regimens to predict clinical outcome. This ability to perform the "virtual clinical testing" of a new drug often gives valuable insight into the optimal trial design for future clinical testing. This tool assists investigators to make better development decisions through a rational and integrated analysis of all the available data when advancing a new project.

PK/PD modeling is the basis of clinical trial simulations.

How to Successfully Implement Modeling and Simulation Strategies

The successful application of a modeling and simulation strategy as part of the clinical development process (from Phase I to Phase III registration trials) needs to be an interdisciplinary approach among clinical pharmacologists, pharmacokineticists, statisticians, project planners and key decision makers on a project team. However, this multidisciplinary approach, focused around a trial simulation strategy can reap benefits by facilitating cross-disciplinary communication, thereby facilitating the utilization of all relevant preclinical and clinical pharmacokinetic, dynamic, safety and efficacy observations as the program develops. A properly executed trial simulation strategy can be viewed, therefore, as a "conduit for communication."

However, the coordination of these tasks can be challenging, and it is important to understand that the approach can be very dynamic in nature, evolving as new information is obtained and fed back into the model. This iterative approach may require a shift in thinking in order to set up processes and procedures to facilitate the availability of new PK and PD information as it emerges during the course of a clinical study. To this end, investigators may have to arrange for PK data to be analyzed in real time and permit the partial unblinding of clinical results to certain key stakeholders involved in the early modeling work. The bottom line is that modeling and simulation does require time, effort and thought in order for it to be successful.

An interdisciplinary approach needs to be taken with clinical trial simulation. Communication is key to this process, which may involve a shift in thinking.

Benefits Gained from Successful Implementation of Simulation Strategies

Trial simulation strategies have been successfully employed to help determine the impact of formulation changes on clinical response and assist in optimal formulation selection based on both pharmacokinetic and pharmacodynamic considerations. Trial simulations have also been successfully used to determine the most robust clinical trial design with respect to study design, patient numbers and number of dose groups, thereby minimizing time and cost. This approach has also been successfully employed to get an early insight on future dosing regimens, thereby expediting protocol development and compressing development timelines. However, perhaps one of the greatest benefits of this approach is the risk mitigation potential it offers in late stage clinical development when the stakes are high. In this setting, the use of modeling and simulation can substantially improve the quality of critical go/no go drug development decision-making and assist in identifying the optimal dose and dosing regimen to take forward into costly registration trials.

While it may be challenging to implement a clinical simulation strategy, the benefits to be reaped from it are enormous.

Summary

As this methodology becomes increasingly more established and accepted within the regulatory, scientific and medical communities, modeling and trial simulation strategies will become increasingly more prominent in drug development programs and regulatory approvals. Although modeling and simulation is a relatively new

discipline to the biomedical sciences, the prospects for future growth and impact in this area are immense.

This paper merely touches the surface regarding how to successfully implement modeling and trial simulation strategies. We can help you with planning a successful simulation project, choosing and implementing appropriate PK/PD models, or other aspects of modeling and simulation.

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