Using PKPD Modeling to **Increase Success in Drug Development Programs**

Highlights:

- Pharmacokinetics (PK) studies the body's effect on a drug
- Pharmacodynamics (PD) studies a drug's effect on the body
- PKPD can reduce dosing errors and adverse effects by accounting for variability
- PKPD can help foster patient-centric trials by reducing sampling and minimizing invasive procedures

Modeling for Efficiency

Although the EMA and FDA very quickly released guidance documents on conducting cliQuantifying biological processes is at the heart of clinical research. Determining how the human body will respond to pharmaceuticals — and whether the desired results will be achieved — are the ultimate goals to finding the right dose for the right patient at the right time. Largely, this comes down to a biological study, but an often-overlooked solution lies in mathematics. Pharmacokinetics (PK) and pharmacodynamics (PD) are modeling techniques that interpret and describe pharmacology quantitively. Applying PKPD modeling can streamline trials, reduce costs, increase patient centricity, and create safer, more efficient trials.

Basics of Pharmacokinetics

PK modeling is a mathematical analysis focused on studying the impact of the human body on a drug. In other words, once a drug enters the body, what happens next? PK studies the absorption, distribution, metabolism, and excretion (ADME) of the drug in each bodily "compartment" — the bloodstream, fatty tissues, muscles, etc. — how they each respond to (and what is there and impact on) that drug as it proceeds through the body.

- **Absorption:** Characterizing the drug exposure, when drug is administered through various routes, quantification of the rate and magnitude of exposure to a drug is critical for determining how much is sufficient to get the desired effect in the clinic.
- **Distribution:** Once the drug is absorbed to the blood stream, PK modeling evaluates the extend of its distribution into body compartments, by quantitatively defining the amount of drug between one compartment to another. PBPK modeling also accounts

for multiple factors that impact the drug distribution, which may include regional blood flow rates, protein binding, molecular size of the drug, polarity, lipophilicity, and permeability.

- **Metabolism:** PK examines any changes the body may make on that drug after it enters the body, to determine whether it's being converted into something helpful or not in the process of formation of metabolites— which may or may not be pharmacologically active, and sometimes more than the parent drug, as in cases of prodrugs
- **Elimination:** Last, PK explores the process in which the body is excreting the drug, examining how much of the primary drug is being eliminated from the body, and in what form or level. Quantifying the rate of elimination helps is estimating the dosing regimens.

Basics of Pharmacodynamics

Where PK focuses on the body's impact on a drug, PD examines the impact of the drug on the human body — namely, what is the body's response? Are you seeing the intended effect of the drug as you were anticipating? The response may be characterized differently by therapeutic area; for example, an infectious disease trial may be focusing on a result differently than a pain or neurology trial. PD explores the complex interactions between the human body, the drug, and any pathogen involved, using calculations to create a reliable model that can be applied to predict results through various relationships (direct/indirect/Emax/Sigmoidal/time dependent etc.).

Benefits of PKPD Modeling

Using PKPD offers the opportunity to design the most effective trial by gaining early insight into dosing, streamlining trials, and increasing the chance for greater safety and efficacy. Since most trials are based on an endpoint and variability around that endpoint, by calculating the PKPD variables (the absorption, distribution, metabolism, and elimination) and their relationship with response endpoints (different biomarkers) and having them fully available for analysis and adaptation, streamlining study planning between phases can occur with greater confidence. Uncertainty is reduced.

Advancing through trial phases, the information becomes increasingly refined using PKPD. Trials can proceed with smaller sample sizes because the source of variability around estimates is identified. Further, these modeling tools helps determine the impact of formulation changes on exposure thus on clinical response and assist in optimal formulation selection based on both pharmacokinetic and pharmacodynamic considerations. Since about 70% of clinical trial failures are attributed to dosing errors, PKPD modeling plays a critical role in accounting for that variability and allowing for the ability to pivot based on its preliminary predictions. All this before access to clinical data, reducing the number of clinical trials needed.

PKPD also offers the potential for risk mitigation in late stage clinical development, where the use of modeling and simulation can substantially improve the quality of critical go/no-go drug development decisions and help identify the optimal dose and dosing regimen to take forward into costly registration trials and labeling.

Patient Impact

PKPD can be beneficial for trials that include special patient populations. With rare disease trials or pediatric and senior populations, for example, the reduced need for sampling can be beneficial from a patient perspective — decreasing the need for multiple sample draws as well as the need for repeated clinic visits through sparse sampling strategy.

As PK serves as a marker for both safety and efficacy, simulations and hypothesis testing also reduces the risk of adverse effects on patients and allow platform for benefit-risk assessment. These tools can be applied to optimize the dosing for organ impairment patient, for example, suppose a drug is metabolized from the liver, but a patient has third stage liver cirrhosis, where the patient's liver is not working at one hundred percent, PKPD modeling can safely help researchers understand what necessary changes are required. What to expect from the PKPD Team?

At Synteract, our PKPD team works as part of our integrated framework to support our clients at different stages of drug development. Our dedicated PKPD team performs analyses using different platform including NCA< PKPD, PBPK, and PopPK in tandem with our regulatory services team, not only providing expert consulting for PKPD, but also the corresponding regulatory aspects for trial design, submission, and regulatory support. We have the ability to execute that trial and bring in the knowledge of clinical operations, so our PKPD services are brought into the conversation from the very beginning, making it a seamless, integrated process.

About Synteract

Synteract®, a Syneos Health® company, is a leading full-service CRO focused on the emerging biopharma segment. The Company's multidisciplinary teams support biotech and pharmaceutical companies across all phases of drug development, providing deep expertise in oncology, dermatology, general medicine, infectious disease and vaccines, neuroscience, pediatrics, and rare and orphan diseases. Synteract has conducted nearly 4,000 studies on six continents in over 62 countries. Contact us if you're interested in learning more or would like to schedule a meeting with one of our PKPD experts.