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TOXICOKINETICS, PHARMACOKINETICS, AND PHARMACODYNAMICS

A closer look at the collection and use of PK/PD data in early phase drug development

The understanding of a new drug's absorption, distribution, metabolism, and excretion (ADME) is critical to ensure that it is safe for human use. That understanding is achieved through collection and analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data, which together account for approximately **25% of the contents of a drug package insert or label**.

The characterization of PK/PD effects starts with nonclinical toxicokinetic (TK) studies in animals. The purpose of TK studies is to define the chemical properties of the drug, including pharmacology and toxicology, and to assist in development of downstream clinical protocols. The necessary nonclinical studies are conducted before submission of Investigational New Drug (IND) applications to the FDA or other global regulatory agencies, and deliver critical data used to set the parameters for future clinical trials.

In this issue, we discuss how the understanding of a novel drug's PK and PD properties begins with nonclinical studies and evolves through early phase clinical trials.

NONCLINICAL STUDIES

For regulatory submissions of a test article, the nonclinical studies that provide initial TK, PK, and PD data need to be conducted in accordance with Good Laboratory Practice (GLP) guidelines. Selection of the most sensitive or relevant species for assessing human risk is a required regulatory element of nonclinical study design. According to ICH Safety Guidelines, the eventual human use parameters regarding dose, route of administration, and duration of exposure must be demonstrated in both rodent and non-rodent species.

ICHS6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals 3.3 Animal Species/Model Selection

Safety evaluation programs should include the use of relevant species. A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies).

IND Requirements and Translation to Clinical PK/PD

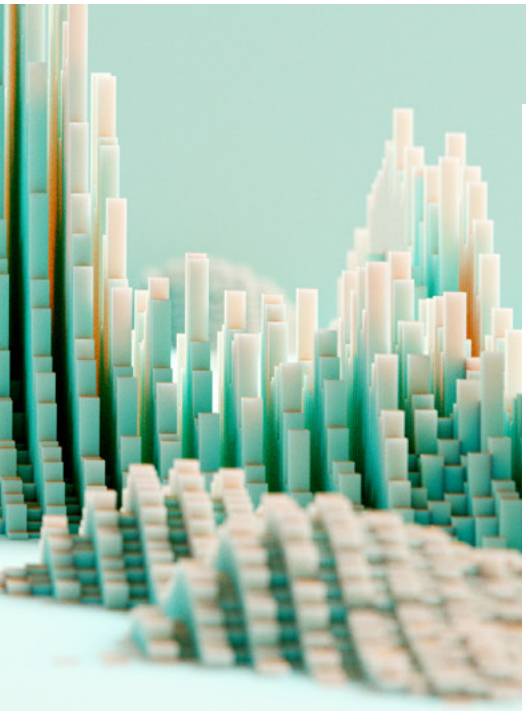
PK/PD ADME analysis relates drug concentration to drug effect; drug effects are determined by drug concentration at the receptors upon which the drug acts. Drug molecules are subject to degradation via metabolism by enzymes, and to removal from the body via excretion by urine, feces, or exhaled air. ADME processes convert a drug dose administered at a single anatomical site and a single point in time into a dynamic range of drug concentrations that rises and then falls throughout the body over time.

The most precise assessment of the relationship between drug concentration and drug effect would measure drug concentrations at the receptor sites.

Since measurement of drug concentration at the receptor can be challenging, and the site of receptors might be unknown or broadly distributed, drug concentrations are generally assessed in more accessible vehicles (e.g., venous blood or cerebrospinal fluid) that approximate drug concentrations across broad areas within the organism.

PK/PD analysis also supports evaluation of the relationship between drug effect and concentrations of the administered drug and its metabolites. In many cases, these metabolites are active and may contribute to the overall effect produced by an administered drug dose. When samples of the chosen vehicle are analyzed for concentrations of the administered drug, they can also be analyzed for concentrations of known or suspected metabolites, and changing drug effects over time can be related to changing concentrations of the metabolites, as well as the parent drug.

Another benefit of PK/PD analysis is that in addition to offering a basis for evaluating changing drug effects over time within an organism, it **allows for evaluation of drug effects between organisms.** The administration of a given drug dose of investigational drug often produces different effects across subjects within a species or across subjects of different species in translational studies.



Metabolism may happen at different rates, or yield different metabolites in different subjects, and these differences will provide a variety of different profiles of drug and metabolite concentrations and associated behavioral and physiological effects over time. Analyzing drug and metabolite concentration as the primary independent variable can reveal PK differences across subjects or species, and provides a basis for integrating these differences into interpretation of drug effects.

Knowledge integration is critical to the design of a **successful PK/PD study, which should include:**

- a range of doses (e.g., 3)
- a range of timepoints (e.g., 5–6 around T_{max})
- a washout phase to assess direct or indirect effects on the target
- measurement of plasma levels and target tissue
- multiple samples from individual animals

Translating Nonclinical Knowledge of PK/PD Analyses to Clinical Study

A sound translational drug development strategy ensures that nonclinical models are meticulously chosen and performed under standard conditions. PK and PD scientists, biostatisticians, and clinical trial teams use the PK and PD data from those studies to inform the design of clinical studies.

When **determining human trial doses**, PK scientists evaluate nonclinical TK data to ensure that clinical trial doses are accurately calculated in agreement with relevant FDA guidance M3(R2) Nonclinical Safety Studies. For example, the maximum recommended starting dose in humans utilizes the nonclinical no observable adverse effect (NOAEL) data in relevant animal species, converted to human equivalent dose. A safety factor is applied in the calculations for the first-in-human (FIH) trial starting dose, to ensure subject safety.

For **dose scaling**, allometric scaling or modeling/simulation with specialized software can be employed. These strategies allow for scaling between species, and modeling enables further simulation between populations, such as pediatric, adult, and hepatic or renal impairment.

Nonclinical data is also utilized to determine which **toxicity assessments** should be planned for in clinical trials (e.g., cardiovascular or gastrointestinal toxicity in animals requires study in humans).

Efficacy PD biomarkers to include in clinical trials are based on nonclinical ***in vitro*** and ***in vivo*** data, showing evidence of the drug hitting its target. This is particularly important in fields such as oncology and neurodegenerative diseases.

For **CNS-active drugs**, a variety of PD assessments are available to more thoroughly characterize cognitive and behavioural impacts. Watch our webinar, Inside the Pharmacodynamic Toolbox, for an in-depth review.

PK/PD Scientists Add Value to Drug Development Processes

Some of the specific tasks a PK scientist may perform include:

- developing and validating analytical methods to measure drug concentrations in biological fluids, such as blood or urine;
- designing and conducting studies to assess the pharmacokinetic properties of drugs in humans or animals;
- analyzing and interpreting data from pharmacokinetic studies; and
- communicating the results of pharmacokinetic studies to stakeholders, such as regulatory agencies or drug development teams.

Overall, PK scientists play a crucial role in understanding how drugs work in the body, and helping to develop safe and effective therapies for a variety of diseases and conditions.

Quality FIH trial designs are critical to the drug development process. They may need to be modified as final nonclinical data becomes available, or after the initial PK data have been analyzed.

ALTASCIENCES' SCENARIO CASE STUDY

The scenarios below describe how the involvement of PK/PD experts use nonclinical data to improve clinical trial design and deliver added value to sponsors. To protect client confidentiality, details are hypothetical. However, the description of expertise and value-added capabilities is based on real activities and delivered solutions.

Introduction – Background:

A pharmaceutical company developing a novel drug contracted Altasciences to conduct nonclinical and clinical studies. The drug was a small molecule, targeting a specific signaling pathway in brain cells. Nonclinical studies had shown promising efficacy and safety profiles, and the company was ready to move forward with a FIH trial.

Drug: novel small molecule drug targeting a specific brain signaling pathway

Indication: anti-seizure

Route of Administration: intravenous (IV)

1. Nonclinical Study Design:

- controlled, three doses SAD/MAD weekly IV bolus
- 28-day rodent (rat); 28-day non-rodent (dog)
- toxicology–emphasis on central nervous system (CNS) and brain tissue assessments
- TK–plasma and brain tissue

Results: Weekly dosing provided adequate drug exposure, achieving anticipated effective levels in plasma and brain, with NOAEL at mid-range dose administered.

2. FIH Trial Design:

- SAD/MAD dose-escalation, double-blind, placebo-controlled
- to evaluate safety, tolerability, and PK
- in healthy normal volunteers

The FIH trial design was established early in the drug development process, based on the preliminary nonclinical efficacy and safety data. The study was designed to evaluate safety, tolerability, and PK in humans at increasing doses to determine the MTD, and inform further clinical development.

PK/PD Scientist Involvement

Altasciences' PK/PD scientists analyzed the final nonclinical PK data and identified unexpected results. They found that the drug was eliminated from the animal models much more rapidly than anticipated, suggesting that adopting a similar dosing regimen in humans might not achieve therapeutic levels.

Study Design Modifications

Altasciences' PK/PD scientists collaborated with our clinical team to propose a FIH trial design that included **more frequent or higher doses** to achieve adequate exposure levels in humans.

PK/PD scientists recommended **increased PK sampling frequency** in the clinical trial to confirm that the drug behaved similarly in humans as in the animal models.

The protocol modifications ensured the FIH trial evaluated the drug's safety and efficacy under conditions likely to achieve therapeutic levels. Additionally, the PK sampling schema allowed for a more complete characterization of the drug's PK profile, which proved essential for dose optimization in subsequent patient trials.

How the PK/PD Team Delivered Value

Altasciences' clinical team relied on their PK/PD scientists' expertise to modify the FIH trial design. The clinical trial demonstrated that the drug achieved desired exposure levels and had an acceptable safety profile. Collaborating to optimize the FIH trial design led to a more efficient and informative clinical development to bring the drug closer to market approval.

HOW ALTASCIENCES CAN HELP

Working with a drug development partner that has integrated nonclinical to clinical capabilities, and their own bioanalytical laboratories, can significantly accelerate the advancement to FIH trials. With fewer handoffs, fewer supplier negotiations, and fewer confidentiality agreements to finalize, data can flow quickly and efficiently to enable agile and flexible drug development.

All of Altasciences' TK/PK/PD services are conducted in accordance with FDA, Health Canada, EMA, and ICH guidelines, and we routinely customize the outputs based on client requests, including the possibility of obtaining interim results. Approximately two thirds of the nonclinical studies conducted at Altasciences are GLP, in support of IND applications. Our PK/PD team is trained to be both GCP and GLP compliant.

Pharmacometric, Pharmacokinetic, and Pharmacodynamic Services

We offer the following expert services in support of your drug development programs:

- data management, programming, and CDISC SDTM and SEND dataset creation;
- design and interpretation of nonclinical and clinical studies;
- noncompartmental PK and TK analysis (NCA), for nonclinical and clinical studies using WinNonlin® (Phoenix);
- analysis plans;
- PK/PD modeling;
- interpretation of PK and PD outcomes;
- dose escalation decisions and review (rapid turnaround in PK analysis and interpretation);
- production of stand-alone PK/PD or input into the clinical study report; and
- comprehensive, submission-ready packages for regulatory authorities.

Working with an expert early phase drug development partner that offers integrated nonclinical to clinical services can deliver significant value and time savings to your programs. With transparent data sharing and early access to results between nonclinical and clinical development, Altasciences' PK/PD team will ensure the most appropriate design for your clinical trials is developed without delay. Supported by our Proactive Drug Development approach, our integrated processes, centralized scheduling system, and streamlined workflows get you safely to clinical proof of concept, faster.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.