

Quantitative pharmacology reduces clinical failure in drug development

Quantitative pharmacology integrates pharmacokinetics and pharmacodynamics to guide candidate selection, optimise dosing and strengthen decisions from preclinical research through clinical trials, reducing development risks and improving therapeutic success rates



The process of discovering and developing a drug to obtain marketing approval is lengthy (8-10 years), risky (~10% success rate), and expensive (~1 billion US dollars). Two major reasons for drug attrition in clinical development, apart from safety, are suboptimal pharmacokinetics (PK) and lack of therapeutic efficacy. The efficacy of a drug depends on the relationship between its concentration-time course (PK) and its pharmacodynamics (PD) (onset, intensity, duration of pharmacological effect). Pharmacological effect at a given dose is quantified by combining the quantitative measures of PK and PD, known as quantitative pharmacology (QP). Consequently, the effective clinical dose should be based on the drug's optimal QP. Hence, it is important to optimise the PK/PD (QP) of a drug candidate as early as possible in the discovery programme to minimise the risks of clinical failure.

A drug discovery programme is planned and initiated based on a clinical need in a

therapeutic area. The properties required for the candidate drug (CD) to treat a disease are defined in a target product profile (TPP). A key goal of the TPP is to set the dose, dose frequency, and treatment duration required to achieve the desired clinical benefit (efficacy) without adverse effects. The preclinical programme prepares a plan to identify CDs with the PK/PD properties needed to meet the dose-related criteria set in the TPP. Apply PK/PD reasoning in preclinical development to strengthen clinical development through learning and confirmation.

Preclinical stage: Lead compound identification is a key milestone in this stage. The lead compound (LC) is a molecule with a combination of potency at the drug target and drug-like properties, expected to be pharmacologically active. This means it should demonstrate efficacy in a preclinical disease animal model supported by QP. When a quantitative PK/PD relationship has been established for the LC, an initial estimate of the

clinical exposure (PK) required for efficacy is obtained. However, failure to demonstrate efficacy (known as proof of concept (PoC) at this stage) can set the project back. A reason for failure could be suboptimal PK (e.g., poor bioavailability at the drug target site in tissues, short half-life). Because the time course of pharmacological responses can be instantaneous or delayed relative to the concentration time course, it is important to understand the temporal relationship between PK and PD. Evaluate compounds based on PK/PD, not PK alone, as this can be misleading and may cause you to miss promising candidates. The QP of the LC forms the basis for lead optimisation, along with safety, to identify the preclinical drug candidate that has the potential to satisfy the TPP.

The PK and PD of a drug can be described (modelled) using mathematical equations that can be integrated with computational methods. Computational dynamic PK/PD models can be developed for the LC in preclinical stages by linking PK and PD models.



These dynamic PK/PD models can predict (simulate) the time course of pharmacological effects for different doses and regimens. They can provide a rationale for selecting the optimum dose and regimen to achieve maximum efficacy. Drug regulatory agencies such as the USFDA and EMA encourage and support PK/PD modelling and simulation for decision-making.

Clinical stages:

In phase 1, the PK and safety of the CD is evaluated with escalating doses in healthy human volunteers or patients. One goal is to determine the dose that produces the appropriate PK associated with pharmacologically active exposures (e.g., unbound C_{max}, AUC) identified in preclinical studies, and to assess whether the PK supports the dose and regimen set in the TPP. Many clinical candidates fail at this stage because they cannot demonstrate the desired PK. Therefore, it is important to predict the CD's PK in humans with reasonable confidence before Phase 1 begins to assess its potential to meet the TPP criteria.

Physiologically-based pharmacokinetics (PBPK) models can predict PK in humans by linking drug-specific properties with system-specific properties using computational methods. PBPK models can be linked to PD models to

predict PK/PD time course in humans. Combining human PK with QP data from preclinical studies can help support dose selection for phase 2 studies. The preclinical dynamic PK/PD model can also be extended to humans to support selection of phase 2 dose and regimens.

In phase 2 studies, efficacy trials are conducted in a limited number of patients using different dose levels or regimens to identify the dose and regimen for registration phase 3 trials. Quantitative analysis of PK/PD relationships with clinical efficacy, using dose-exposure-response or PK/PD modelling, can help select the dose and regimen for phase 3 studies. Population PK models can be developed during phase 2 studies to understand how demographics (age, sex, race) and comorbidities (impaired liver or kidney function) influence CD PK. This helps select the right dose for the population.

In registration (phase 3) studies, the CD's ability to demonstrate significant efficacy, in addition to safety, is tested in a large number of patients. This requires that the dose selected for phase 3 be strongly supported by PK/PD reasoning from phase 2 trials. When the CD demonstrates clinical efficacy, confirm that robust PK/PD relationships drive efficacy. Population PK/PD models built in phase

2 can be strengthened with phase 3 data and used to identify appropriate doses for specific populations. Dose and regimen decisions should be based on a strong PK/PD rationale to support marketing approval.

Use PK/PD (Quantitative Pharmacology) for critical decision-making from preclinical through clinical stages of drug development to minimise the risk of drug candidate failure. QP is the basis for setting dose, regimen and duration of treatment for an approved drug.

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