**Executive summary**

In their efforts to transform clinical development, biopharma firms need to improve go/no-go decision-making to improve portfolio productivity. This relies on improving insights from early-phase trials, including first-in-human (FIH) studies, designed to evaluate a candidate product’s tolerability, pharmacokinetics and pharmacodynamics.

Strategies for dose escalation at this stage are critical for volunteer safety and for study success. Decisions regarding dose escalation involve balancing three elements: risks to individual volunteers; risks of failing to identify the correct dose range to use in subsequent studies; and risks of delaying or stopping development of a potentially useful product. Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation offer a set of tools to increase the predictability of drug candidate performance. By identifying the best individualized dosing regimen to treat a given indication, patient outcomes can be improved, and the probability of a molecule’s success can be increased.
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Introduction

As they work to transform clinical development, biopharma companies face challenges from many directions. Pipeline pressures are intensifying the demand for speed and productivity, requiring companies to improve decision-making regarding which compounds to move forward through the development process. The resulting need for portfolio productivity requires improved early-phase studies that deliver optimum quality and quantifiable data for insights to make the correct decisions in developing a successful portfolio. In this environment, new approaches are needed to better gauge an investigational drug’s viability and facilitate better go/no-go decisions.

Clinical considerations for dose escalation studies

Determining the best dose escalation scheme in first-in-human (FIH) studies is important and challenging. The design for FIH studies in healthy volunteers can appear arbitrary at times. There is a great deal of guidance on starting doses in humans with definitive stopping rules. Yet the approaches used for dose escalation – the number of dose levels, escalation methods, cohort sizes and distribution – vary widely within the industry.

The purpose of most Phase I studies is to understand a candidate product’s tolerability, pharmacokinetics and pharmacodynamics (Figure 1). This information is then used to inform the decision on whether to continue or stop further development.

Figure 1: The purpose of most Phase I studies

First dose calculation requires extensive deliberation, and the rules are well established. Strategies regarding dose escalation are also critical for volunteer safety and for a successful study.

Decisions regarding dose escalation involve balancing three elements: risks to individual volunteers; risks of failing to identify the correct dose range to use in subsequent studies; and the risk of delaying or stopping development of a potentially useful product. No two situations are the same and each case requires consideration of numerous factors.
Determining the right strategy

In study design, factors to consider include:

- Use of a sentinel group, stagger dosing
- Appropriate scheme for dose escalation (e.g., linear/arithmetic/log/modified Fibonacci/other)
- Preclinical dose response curve
- Understanding of the pharmacology, but being aware of interspecies variation in translation of results from animal models to humans (sometimes, what is seen in vitro will not be reflected in vivo)
- Potential toxicity and whether its impact is mild or serious (e.g., sedation vs. cardiac arrhythmias)
- Predicted pharmacokinetics
- Comparison with similar drugs already administered to humans to help identify potential toxicological effects
- Ability to measure “early warning” biomarkers
- Previous cohort data on exposure, effect and safety
- Need for the protocol to give clear instructions but allow flexibility around the stated rationale (a flow diagram or algorithm can be helpful here).

During protocol writing, there may be the option to switch from healthy individuals to patient volunteers within the same protocol based on achievement of a pre-defined endpoint. Rules for dose escalation may change within the same protocol. Each protocol must provide the following three specifications for dose escalation. First, the minimum data set and the number of subjects required for dose escalation. Second, a clear set of stopping rules for the individual subject, the cohort and the study. Third, PK and biomarker data at pre-specified dose levels and time points when such data are pertinent to guiding the next dose. The protocol must describe who is responsible for reviewing the data and who, if anyone, is unblinded. If a suspected unexpected serious adverse reaction (SUSAR) occurs, unblinding of that subject’s medication is mandatory. The Principal Investigator is responsible for determining the next dose following the protocol’s guidance with volunteer safety as the priority.

In study conduct, before proceeding, between-cohort review must take account of information on exposure and response (safety and effectiveness, if available) from the preceding human dose. This includes data on: subjective/objective adverse events (type, severity, duration, action taken, outcome, likelihood that they are attributable to the study drug); vital signs, ECG (for example, QTc); laboratory data, including blood and urine testing, and other safety tests; and PK and PD measures as appropriate. Great care must be taken not to rely extensively on mean data when planning the next dose, as the outlier may be the subject at most risk.

An example decision algorithm is illustrated in Figure 2, which includes a three-level safety grading scale to support dose escalation and define stopping rules for healthy subject FIH studies.¹
When to stop

The rules for stopping dose increases should be specified in the protocol and adapted as needed. The most important reason for stopping is the risk to volunteer safety. The maximum planned dose or blood concentration is usually higher than the expected therapeutic dose or blood concentration because of the need for a safety margin, but determination of the maximum tolerated dose should not be the mandatory endpoint. Stopping may also result when the maximum planned pharmacodynamic effect has been achieved or due to unfavorable pharmacokinetics. Examples might include insufficient bioavailability, unacceptably short half-life of the active moiety, excessive inter-individual variability in pharmacokinetics, or emergence in humans of metabolites not adequately covered in the pre-clinical testing.

Dose escalation is a key part of FIH study design. It is important to make use of all available data to inform sensible decisions that protect the safety of the subjects while still achieving the scientific objectives of the study. As experience has shown, even drugs that are extremely well tolerated and safe at low dose, such as paracetamol (acetoaminophen), may cause severe toxicity and death at higher doses.

PK/PD modeling and simulation considerations for dose escalation studies

Overall, modeling and simulation offers a set of tools to advance innovation and healthcare practice, to help manage complexity – in both disease process and human biology – and increase the predictability of drug candidate performance to enable allocation of research investment. The use of PK/PD modeling and simulation to identifying the best individualized dosing regimen to treat a given indication improves patient outcomes and increases the probability of success for a molecule.

This is especially true in early clinical development, where little is known about the relationship between dose and the resulting exposure levels. While some molecules exhibit linear or proportional relationships between dose and exposure levels (e.g., double the dose = double the exposure) over a given range, many molecules also show evidence of a nonlinear relationship (e.g., double the dose ≠ double the exposure) in the dose versus exposure profile. This is often due to saturable transport mechanisms. For molecules displaying nonlinearities in the link between dose and exposure, predicting exposures for a dose to be administered in a subsequent FIH dose escalation study cohort can be a difficult task.

“All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.”
– Paracelsus, 1493-1541
The initial learning phase generally starts during the FIH dose escalation studies in determining the maximum tolerated single or multiple dose exposures. Two or three FIH dosing cohorts are often required to have sufficient data to start informing the PK/PD model. While a simple, two-stage compartmental PK modeling effort can be used, development of a nonlinear mixed-effects PK model is preferable to estimate the PK variability between subjects.

The “learn and confirm” paradigm

The “learn and confirm” paradigm concept introduced by Lewis Sheiner provides a framework for iterative learning throughout the clinical development lifecycle. This methodology allows for questions to be asked and answered via the following cyclic process (Figures 3 and 4):

- Aggregate existing data
- Develop a model
- Run simulations based upon the model to inform study design elements
- Execute the study design elements to yield new knowledge and data for model refinement to drive decision-making.

Applications of this iterative process can be utilized between cohorts of a study (e.g., adaptive design), between studies, and/or between phases.

Figure 3: The “learn and confirm” paradigm applied to drug development

Figure 4: The “learn and confirm” paradigm replaces the concepts of Phases I-III

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Conclusion

Identifying the best dose escalation scheme in first-in-human dose escalation studies is a critical and often underestimated step in early development decision-making. Selecting the wrong next dose and approach for escalation can ruin a study, cause unnecessary patient safety risks, waste time and money, yield useless data and contribute to poor go/no-go decisions.

An appropriate strategy to study design, protocol writing and study conduct can provide input to a decision algorithm supporting dose escalation and defining stopping rules, as discussed above. PK/PD modeling and simulation holds promise in helping to manage complexity and increase predictability of the development process by correctly identifying the right dose. The “learn and confirm” paradigm builds on this to provide a framework for iterative learning throughout the phases of clinical development, whereby the confirmation study only takes place once effectiveness and an acceptable benefit/risk balance profile are fully recognized. Overall, such model-based drug development can inform strategy, trial design and decision-making to optimize the probability of success.

As more data are obtained through ensuing cohorts and studies, the PK/PD models can be revised to improve the dose-exposure-response predictions. In fact, this iterative process can continue through Phase I into proof of concept Phase Ila trials and beyond into Phase IIb/III dose-finding studies. Overall, getting an early start on the PK/PD models provides a solid foundation for future Model-Based Drug Development activities – such as clinical trial simulations, trial execution models, decision/scenario analyses, and portfolio/program designs (see Figure 5) – to aid in quantitative decision-making.

Figure 5: Model-based drug development as an aid to improved quantitative decision-making

References


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After completing an Honours degree in Pharmacology and graduating in medicine from Guy’s Hospital in 1979, Professor Tim Mant trained at various London hospitals in Internal Medicine, Clinical Pharmacology and Human Toxicology. He was one of the founders of GDRU (Guy’s Drug Research Unit). His major activity at Quintiles has been as Principal Investigator for the investigation of new chemical entities in humans. In addition to research, he maintains teaching and clinical activities. Professor Mant has published more than 60 articles relating to Clinical Pharmacology and Human Toxicology cited on PubMed. He has co-authored the three most recent editions of A Textbook of Clinical Pharmacology and Therapeutics (Ritter, Lewis, Mant & Ferro) and the accompanying Questions for Self Assessment (Mant, Lewis, Ritter & Ferro), Arnold Publications. He was appointed Visiting Professor at King’s College London School of Medicine at Guy’s, King’s and St Thomas’ Hospitals, London in January 2008. Professor Mant is Honorary Consultant Physician at Guy’s & St Thomas’ Hospital NHS Foundation Trust. He is an examiner for the Diploma in Pharmaceutical Medicine, was an MBBS examiner and lectures on BSc, MSc & MB courses at King’s College London. He is an Educational Supervisor for Postgraduate Training in Pharmaceutical Medicine in the U.K. and is the Organiser for the Advanced Human Pharmacology Course in Exploratory Development and Phase I Studies at KCL. He was the instigator of the first Intercalated BSc programme in Translational Medicine, which started at KCL in 2009. Professor Mant is co-lead for the Experimental Medicine and Therapeutics Cluster at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London’s Comprehensive Biomedical Research Centre funded by the NIHR.

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