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“Where do I start?”: Strategies for selecting the first dose for human clinical trials

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A blank page can be daunting.

> The principal goal of dose selection should always be to safeguard the wellbeing of the study participants.

Knowing where to start is always a challenge, and selecting the initial dose of an investigational drug to be administered in the first clinical study in humans is no exception. Getting it wrong could endanger the lives of the people participating in the study, as well as potentially derailing the whole development program and ruining years of work. The principal goal of dose selection should always be to safeguard the wellbeing of the study participants, often described as picking a "safe" starting dose. However, "safe" should not be interpreted as zero risk, but rather that the level of risk is appropriate and the overall benefit:risk assessment is favorable. A robust dose selection strategy therefore requires a quantitative approach.

First principles

All drugs carry risks of unwanted side effects or toxicity. The presumption is that all toxicity is the consequence of pharmacological activity, whether that be exaggerated primary pharmacology (i.e. an excessive effect on the intended target in the intended location), secondary pharmacology (i.e. an effect on the intended target in an unintended location) or tertiary pharmacology (i.e. the effect on an unintended target, also termed "off target" effects). The molecular target and location may be known or unknown, but in each case, pharmacology is linked to engagement of a target by the drug. The size of the effect reflects the drug concentration at the site of the target ("receptor theory" and "target concentration strategy", see Rang 2006 and Holford 1995). While these principles were first postulated for small molecules, they can also be applied to large molecules and – in principle – emerging therapeutic classes such as antibody-drug conjugates, nucleic acids, etc. Therefore, by quantifying the relationships between dose, exposure, and response, it is possible to predict pharmacological effects based on the dose administered.

Conceptual framework

Selection of a starting dose is not performed in a vacuum. Drug development is a highly regulated process, and national and trans-national regulatory guidelines contain relevant advice for entry-into-human studies (Figure 1). Considered together, these guidelines provide a simple conceptual framework on which to base starting dose selection. The framework consists of four sequential parts: characterization of the pharmacological effects in vitro and in animals, prediction of human exposure, prediction of human response, and mitigation of potential risks arising from unknowns and uncertainties (Figure 2).

Figure 1 - Regulatory guidelines provide a conceptual framework

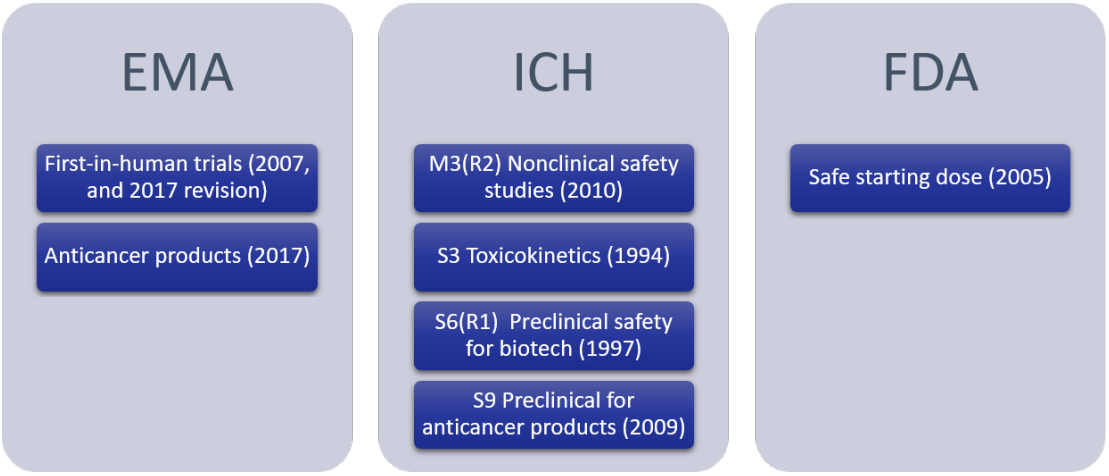
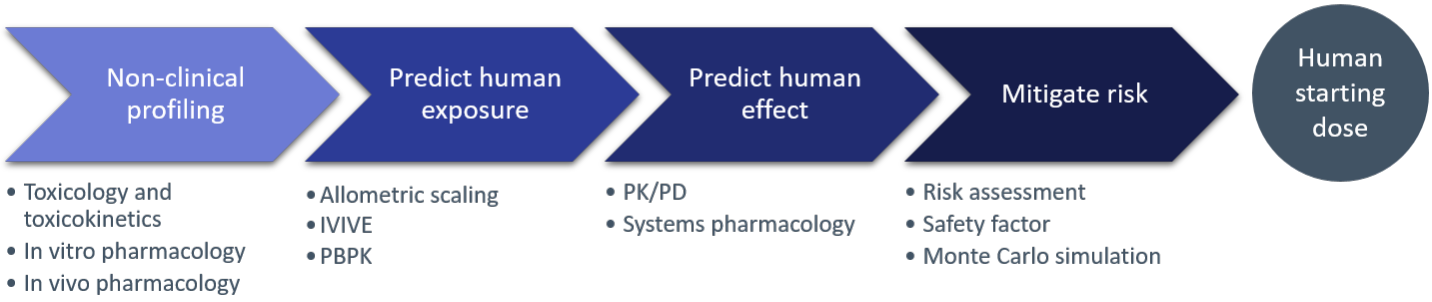


Figure 2 - Conceptual framework



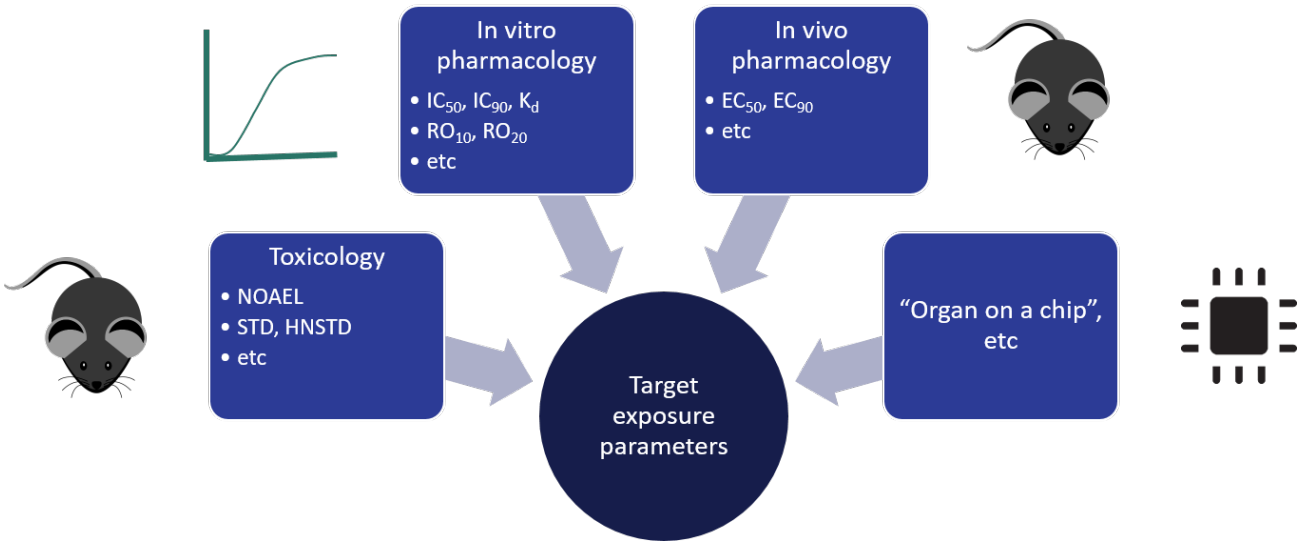
Non-clinical toxicology and pharmacology

Non-clinical toxicology studies remain integral to starting dose selection for all drug development programs. Before administering an investigational compound to humans, it is essential to establish the in vivo toxicity profile in animals in at least one pharmacologically-relevant species (i.e. the intended molecular target is present and is bound by the drug). Toxicology studies have the advantage of being hypothesis-free, meaning that they can address both expected and unexpected pharmacological effects. Nevertheless, they should also be accompanied by in vitro and in vivo pharmacology studies focusing on the effects on defined molecular targets or pathways. These can either be the intended target, or, in the case of safety pharmacology studies, a standard battery of receptors, enzymes, etc. known to be important in key biological processes.

New methods and technologies are also emerging, e.g. “organ-on-a-chip”, which attempts to replicate the physiology of a whole organ in vitro. Use of these alternatives is likely to increase in the future. These approaches can be readily incorporated into the same framework alongside standard toxicology and pharmacology studies. While all available data should be considered, greater weight can be given to those experiments considered most relevant for the mechanism of action.

All experiments should include a measurement of drug concentrations to determine the level of drug exposure that produces a relevant pharmacological effect. The parameters will be different in each type of experiment (e.g. AUC, IC_{50}, EC_{50}, etc.) but each can be translated into a corresponding pharmacokinetic exposure parameter (e.g. AUC, C_{max}, C_{min}, etc.) to serve as a reference value applicable to human dosing.

Non-clinical toxicology and pharmacology



Extrapolation of non-clinical data from animals to humans has historically focused on dose, as exemplified by the US FDA guidance from 2005 which described a method for allometric scaling of animal doses to humans based on relative body surface area (CDER 2005). An advantage of that approach is that it is simple and easy to implement (e.g. Nair et al. 2016). It has, however, been largely superseded by more complex methods which have better predictive performance, although it is noteworthy that scaling of dose by body surface area is still the preferred approach for development of cytotoxic drugs in oncology indications (e.g. Hansen et al. 2015). Measurement of drug concentrations in toxicology and pharmacology studies is crucial because it allows inter-experiment and inter-species comparisons of exposure rather than dose.

Prediction of human exposure

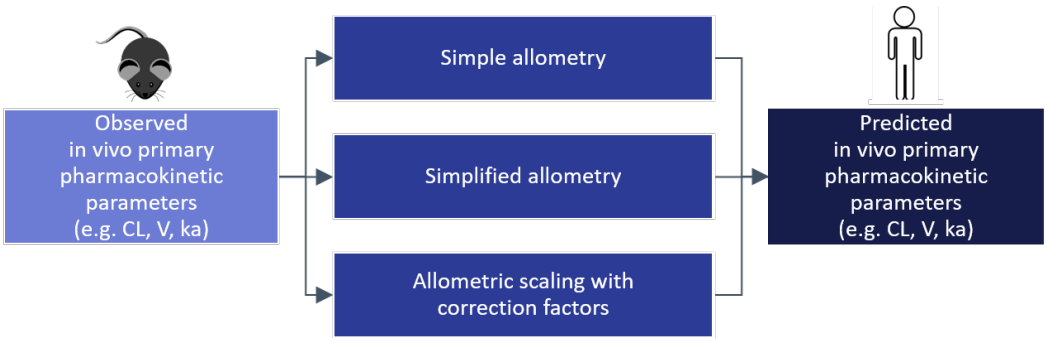
Allometric scaling

Allometry is the study of the relationship of body size to anatomy and physiology, while allometric scaling is the scaling of biological process according to body size, e.g.:

parameter = a x bodyweight^b
where a is a scaling factor and b is an exponent

Allometric scaling in the context of dose selection is the use of mathematical relationships to predict human pharmacokinetic parameters from corresponding animal parameters. There are numerous methods, reviewed by Choi et al. 2019, Wang et al. 2016. In brief, methods fall into three broad categories (Figure 3). There is no single "right" method, and the approach used is often dictated by the preferences of the person doing the analysis. However, it is noteworthy that simplified allometry has the advantage of only requiring data from one animal species.

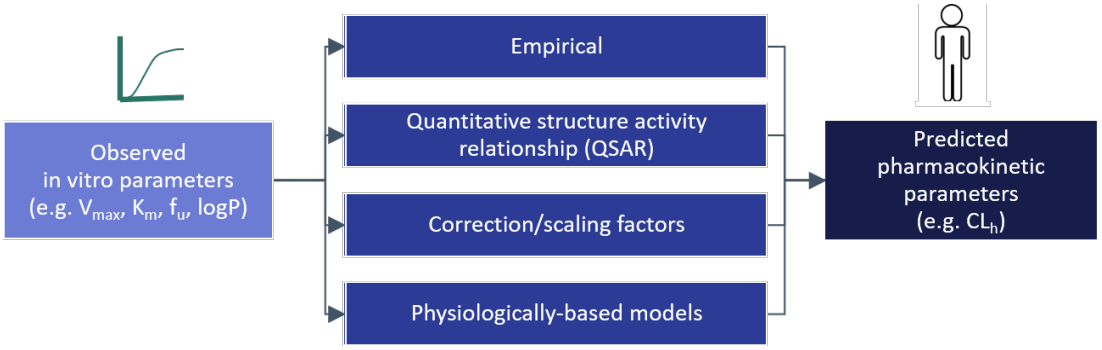
Figure 3 - Allometric scaling



In vitro-in vivo extrapolation

Whereas all allometric scaling is based on in vivo data, an alternative approach is in vitro-in vivo extrapolation (IVIVE) where in vivo parameters are predicted from in vitro studies. Again, there are numerous possible methods, which fall into four broad categories (Figure 4). Some methods are purely empirical, using observed numeric relationships to link in vitro and in vivo parameters. A well-known example is "Lipinski's rule of 5", which is, in essence, a prediction of oral bioavailability based on the chemical structure and lipophilicity of small molecules. Other methods build on the fundamental concepts that underpin the discipline of pharmacokinetics (see Choi et al. 2019 for a review). An example is the "well stirred" model of hepatic clearance, which uses estimates of intrinsic clearance, protein binding, and blood flow to predict hepatic clearance. Most recently, the use of physiologically-based pharmacokinetic (PBPK) models has been adopted.

Figure 4 - In vitro-in vivo extrapolation (IVIVE)

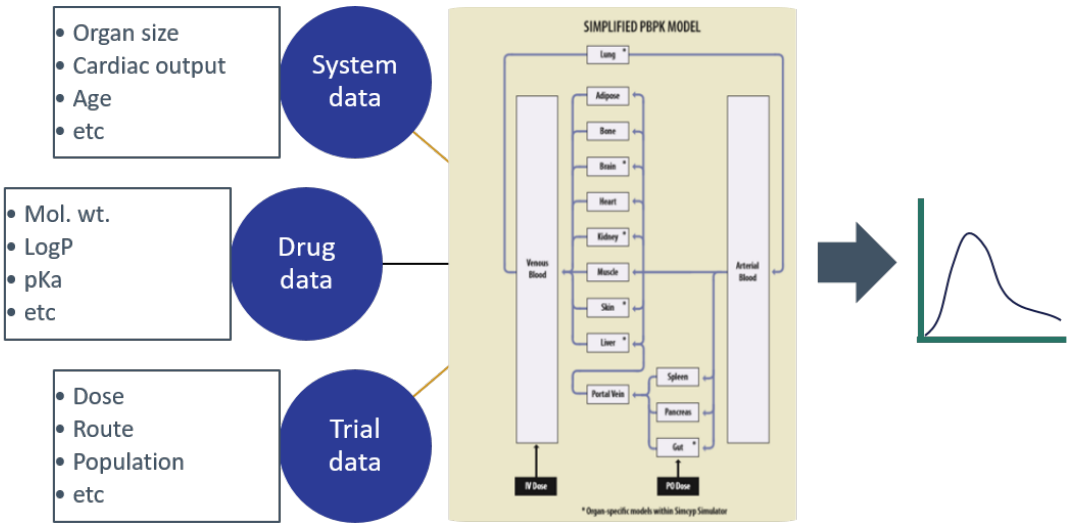


> "It is feasible to use standardized in vitro experiments and PBPK modeling to predict human pharmacokinetics very early in a drug discovery program."

Physiologically-based pharmacokinetic modeling

What is commonly referred to as PBPK modeling can be more accurately described as mechanistic IVIVE linked to a PBPK model (Jamei 2016, Jones et al. 2013, Miller et al. 2019). The PBPK model represents the body as a series of discrete but interlinked organs, each with a defined set of characteristics such as size, blood flow, etc. This model is augmented by data on the physiochemical characteristics of drug, which is extrapolated to predict pharmacokinetic processes within each organ. On top of this is added a third layer of data representing the "real world" scenario to be simulated (e.g. trial design). Integrating these different elements thereby allows simulation of time course profiles for drug concentrations in plasma and tissue, and techniques have reached a level of sophistication that there is an appropriate level of confidence in the reliability of these predictions (albeit still with certain caveats and constraints, Jones et al. 2015, Miller et al. 2019). Adoption of PBPK modeling for starting dose selection has been facilitated by the availability of modeling and simulation tools as "off the shelf" commercial software packages (e.g. Simcyp® Simulator). In addition, because these tools have a clearly defined set of input parameters, it is feasible to use a combination of standardized in vitro experiments and PBPK modeling to produce robust predictions of human pharmacokinetics very early in a drug discovery program.

Figure 5 - Physiologically-based pharmacokinetic modeling (PBPK)

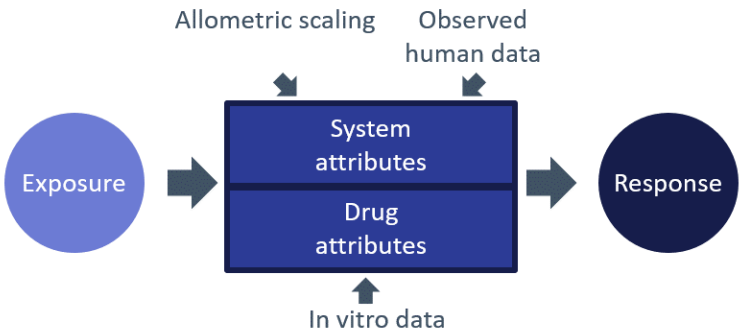


Prediction of pharmacodynamic effects in humans

If making a dose selection based on predicted drug exposure alone, there is the implicit assumption that the exposure vs. response relationship is the same in animals and humans. However, this is often not the case, and explicit prediction of pharmacodynamic effects is required. Methods will be specific to the molecular target of interest and the investigational drug's mechanism of action. It is difficult to generalize. However, any approach has to include attributes of the biological system and attributes of the drug and pharmacologically-active metabolites (Figure 6). It is increasingly being recognized that accurate prediction requires an in-depth knowledge of the biological system and quantitative models that describe it in mechanistic terms. Here quantitative systems pharmacology (QSP), a relatively new scientific discipline that combines systems biology with pharmacology, appears to offer potential (e.g. Sorger et al. 2011).

> "dose selection based on predicted drug exposure alone assumes that the exposure vs. response relationship is the same in animals and humans. However, this is often not the case."

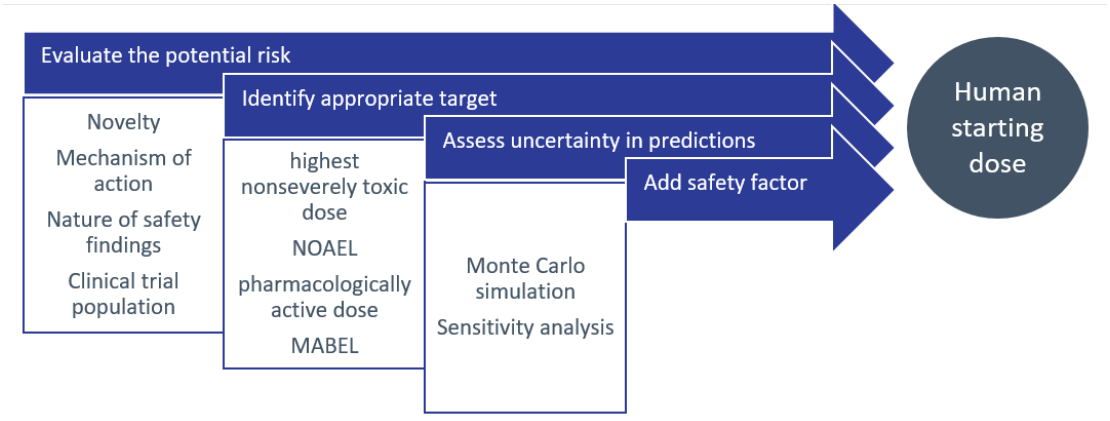
Figure 6 - Pharmacodynamic effects



Risk mitigation

When a prediction of human exposure and response has been made, an appropriate amount of "wiggle room" must be built in to allow for uncertainties and unknowns (Figure 7). This requires a subjective assessment of the level of potential risk, taking into account factors such as the mechanism of action, seriousness of potential side effects, etc. For example an investigational drug which has a novel molecular target would be considered higher risk than an addition to an existing class of drugs (see CHMP 2017). Based on this risk assessment, an appropriate exposure target can be selected. Many Sponsors, especially those in Europe, now focus on the minimum anticipated biological effect level (MABEL) estimated from pharmacology studies rather than the no observed adverse effect level (NOAEL) observed in toxicology studies (e.g. Saber et al. 2016). Finally, a "safety factor" is applied. A traditional rule-of-thumb was to incorporate a 10-fold safety factor, but it is now common to use a bespoke safety factor based on the pharmacokinetic and pharmacodynamic models used in previous steps. Monte Carlo simulation methods where variability is added to each model parameter, or sensitivity analyses where individual parameter values are systematically varied, can be used to derive a plausible range for predictions, which then informs the size of safety factor needed.

Figure 7 - Risk mitigation



Summary

Choosing an appropriate starting dose for the first clinical study in humans requires a quantitative approach to predict human drug exposure and response. I have described a four-part conceptual framework for dose selection, and outlined the methods and tools that can be used to extrapolate in vitro and animal data to humans. There are numerous potential approaches, and no single "right" option. Methods continue to evolve, and use of sophisticated modeling and simulation methods, such as PBPK modeling or quantitative systems pharmacology, is likely to increase. But in all circumstances, planning a strategy in advance will help to remove the mystery from dose selection.

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