

Traditional vs Adaptive design of Phase I/II hybrid trials in Model Based Drug Development (PKPD Modeling)

Krishna Gopal, Ph.D., IQVIA

Vishnu Dabbiru, Independent Consultant

Background

The objective of a typical Phase I/II hybrid design is to establish MTD (Maximum Tolerated Dose), based on observed Dose Limiting Toxicities (DLT). This establishes the RP2D (Recommended Phase II dose). The expansion cohort allows the testing of the RP2D dose level in a slightly larger cohort of subjects to study the effect size. Study designs explicitly for the purpose of determining exposure-response and their relative strengths and limitations are listed in ICH E4. A typical hybrid Phase I/II study data provides valuable input for PKPD modeling, irrespective of design.

Dose finding Phase I trials incorporate cohorts of subjects at different dose levels. The data from these studies have been used to help develop an empirical PKPD model for Dose-Response relationship. Traditional PKPD models assume a receptor mediated mechanism, and based on mode of drug administration, a one or two compartment model.

Adaptive designs in relation to PKPD model development are not well understood. We will seek to understand each of the underlying items and evaluate how each affects the PKPD model building.

Pharmacokinetics (what body does to the drug) and Pharmacodynamics (what drug does to the body)

A- Absorption – Getting the drug into the body

D- Distribution – Distribution into and out of tissues

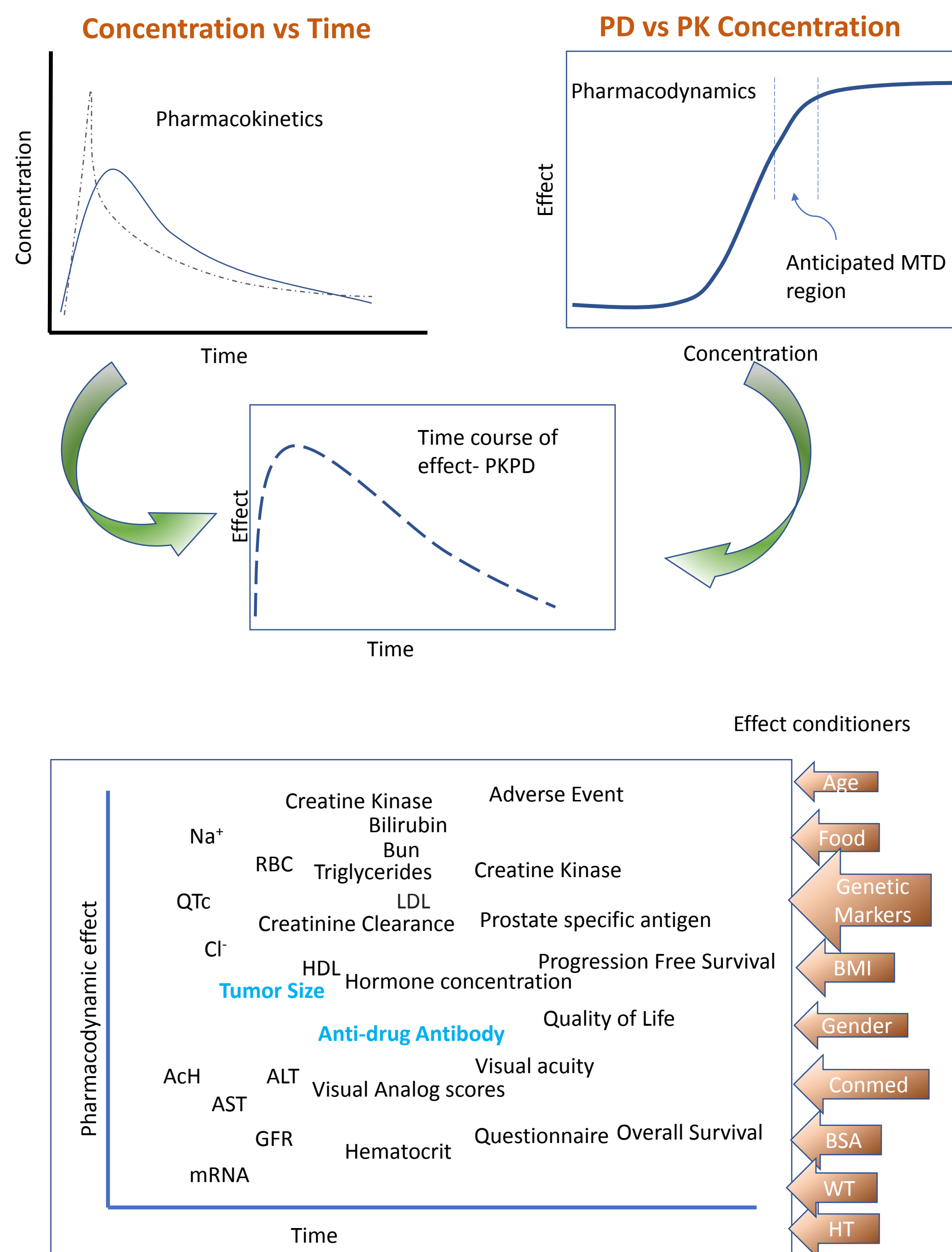
M- Metabolism – Drug-breakdown/transformation to other molecules

E- Excretion - Removal of drug from body

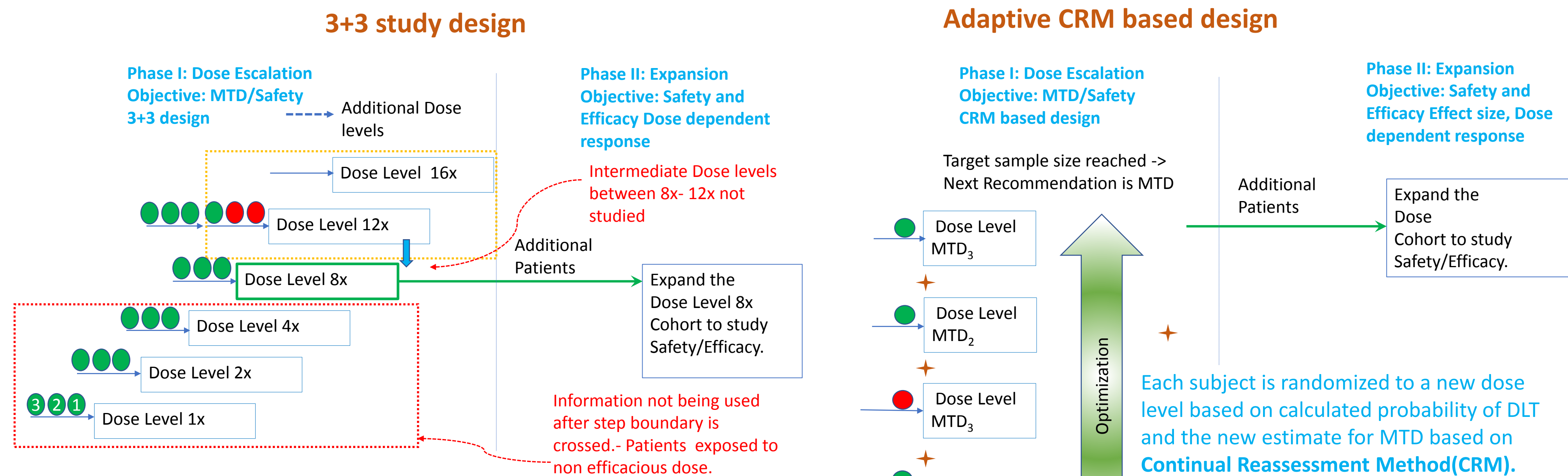
T- Toxicity - Parameter which limits the doses that can be studied.

A POPPK model seeks to establish a relationship between concentration of drug (typically blood) and the administered dose, and describe mathematically a mechanism of drug ADME within the body. The conditioning variables such as age, gender, body surface area etc. help make the model more robust.

A PKPD model seeks to model the relationship between the observed Pharmacodynamic effect and the underlying pharmacokinetic profile of the drug, resulting in a mathematical description of time-course of effect for a given administered dose. The conditioning variables such as age, gender, body surface area etc. help make the model more robust.

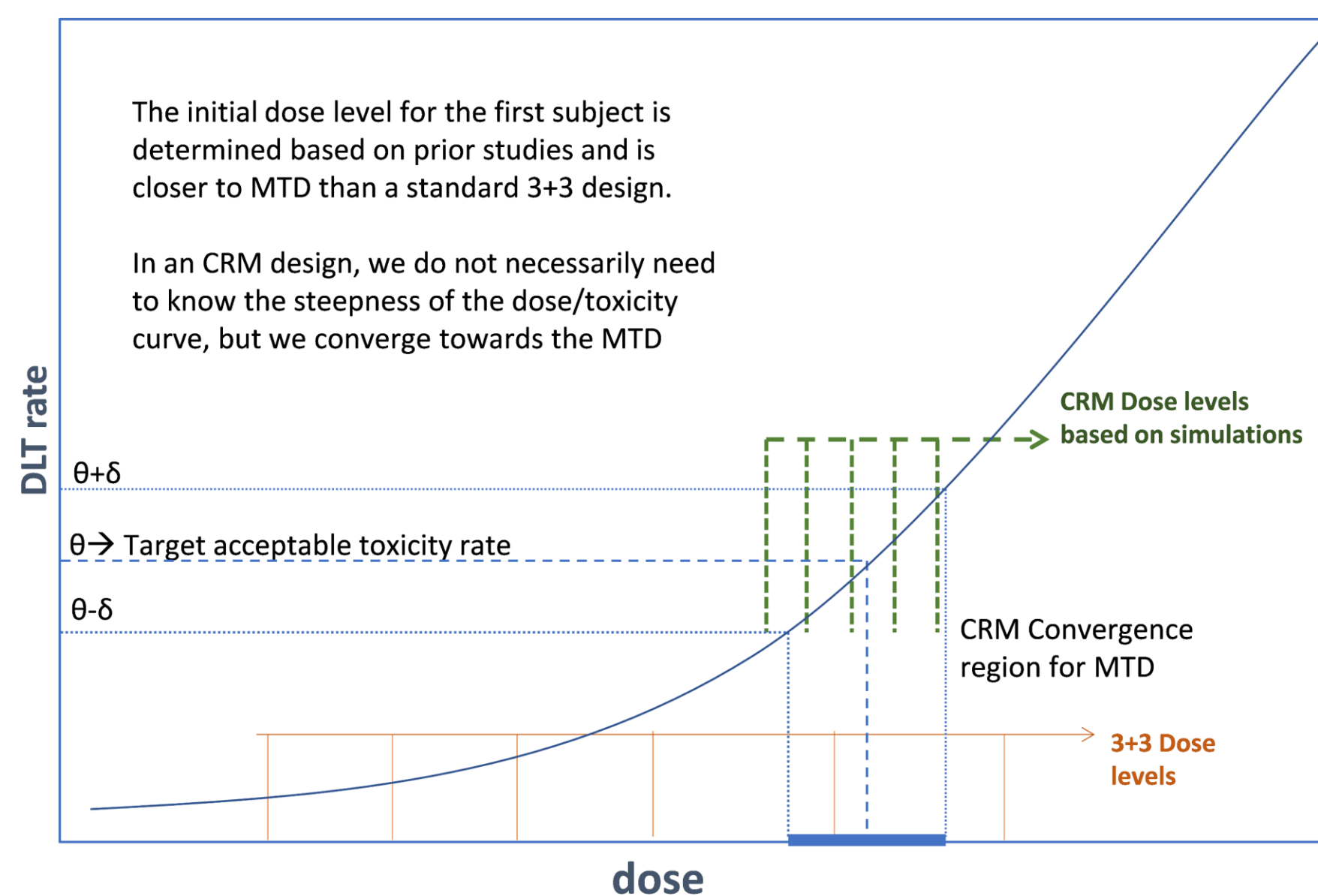


The Pharmacodynamics of a drug are often complex, and all the effects of the study drug are not readily identified. The PKPD model seeks to simplify the process by identifying the **key effect(s) that we seek to influence** which correlate to the disease under study. The measured changes in the effect can be used to correlate to the disease status. This enables a PK scientist to develop a simpler model that could be used to recommend doses and predict outcomes by extrapolation, under different trial conditions. The models are imprecise, and are useful under very specific circumstances.



If there are no Dose Limiting Toxicity (DLT) (AEs), 3 new patients are enrolled at each new dose level. If a DLT AE is observed at a dose level, 3 additional subjects are enrolled at that dose level to see if 2 DLT events occur. If 2 DLT events occur in a 6 subject cohort, MTD is reached and the prior dose would be selected as the MTD. In the hypothetical example above Dose level 8x would be considered MTD. Otherwise, the next higher dose cohort is enrolled.

True dose-toxicity curve



Discussion:

Adaptive designs in clinical trials are gaining popularity and recent literature reviews indicate a growing interest in adaptive designs for clinical trials. PKPD analysis are not typically the primary objective of a trial design when conducting a Phase I/II hybrid design. They are secondary or tertiary objectives.

Between 1991 and 2006, 1.6% of Phase I cancer trials were based on a model based design⁵, this has increased to 6.4% between 2012-2014⁶. Both FDA¹ and European regulators have encouraged the use of adaptive designs during the early stages of drug trials due to the extremely high failure rate of the larger pivotal phase III trials, making the adaptive design trials more lucrative. The main challenges in implementation of new designs stem from unfamiliarity and lack of training of personnel in these new techniques.

PKPD models are typically developed with data gathered from Phase I and II trials and are required² per ICH E4 Guidance. PKPD models conceptualize the entire body system into different compartments, and account for fixed and potentially confounding effects due to inter-subject and intra-subject variability. The quality of the PKPD model depends on the quality of underlying data used to prepare the model. Both empirical and mechanistic models can be developed to describe the observed data. An Empirical model describes the data without biological meaning, and can make interpretation of parameters challenging. These are still useful when designing studies to approximate future exposure-response relationship. Mechanistic models reflect underlying physiological and bio-chemical processes, and have a better predictive power. It is not always easy to develop a mechanistic model, as it requires a clear understanding of the Mechanism of Action.

A greater emphasis during the study design to ensure appropriate development of a robust PKPD model ensures the study's usefulness in not just planning a subsequent pivotal trial within the same patient population, but also provides better predictions for related therapeutic areas and/or patient populations. e.g. extrapolating the data for pediatric studies, or exploring new therapeutic areas.

An adaptive design for Phase I dose finding designs using CRM is well understood and has been found superior to a standard 3+3 design when estimating MTD. However such a design limits the accuracy of both the POPPK and the PKPD (assuming effect/response is collected) model for high and low doses, particularly so, when the CRM model results in a narrow dose range for the study. So although an Adaptive design is more effective than a traditional 3+3 design for identification of the MTD, it is typically less useful when developing a NONMEM POPPK or PKPD model, unless dose range is carefully selected for model development, or a hybrid approach is used. Even then, the outcome randomization dose levels are not well established and there is a likelihood of not studying doses which could have an impact on the PKPD model.

Ethical considerations require the best treatment dose level for the enrolling subject. Not allowing for a wider dose range to be studied, with the understanding that some of the doses may not be optimal, reduces the usefulness of the data for model building. Therefore there needs to be a balance during decision making to ensure that both Individual benefits and common benefits are equally covered.

Tools for Implementing CRM/Adaptive Designs:

- 1) R (crm, bcrn, dferm), standalone R functions
- 2) Winbugs
- 3) Openbugs
- 4) SAS

Efforts for collaboration:

- 1) PhRMA, Pharmaceutical Research and Manufacturers of America
- 2) BIO, Biotechnology Industry Organization

References:

- 1) 2010 draft FDA Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics
- 2) ICH E4, Dose-Response Information to support Drug Registration
- 3) O'Quigly J, Pepe M, Fisher L; Continual Reassessment method: A practical design for phase I clinical trial in cancer, Biometrics, 1990
- 4) Chow SC, Chang M; Adaptive design methods in clinical trials - A review. Orphanet Journal of Rare Diseases, 2008
- 5) Rogatko A, Schoenck D, Jonas W, Tighiouart M, Khuri FR, Porter A; Translation of innovative designs into phase I trials. Journal of Clinical Oncology 25(31), 2007
- 6) van Brummelen EMJ, Huitema ADR, van Werkhoven E, Beijnen JH, Schellens JHM; The performance of model-based versus rule-based phase I clinical trials in oncology. Journal of Pharmacokinetics and Pharmacodynamics 43, 2016

Acknowledgements: Toby Batten, IQVIA and Janet Hathaway, IQVIA, for their review.