

Dose – Exposure – Response Relationships: the Basis of Effective Dose-Regimen Selection

Model-Based Solutions to a Calibration Problem

Michael Looby, Novartis

Peter Milligan, Pfizer

Dose Regimen Selection: the High Development Hurdle

- Optimal dose selection attempts to select **drug input profiles** that offer the best compromise between benefit and risk for a given indication in a given population.
 - The ultimate aim is to tailor dosing to the individual patient, though we are still far from attaining this goal as often as we could or should.
- Typically efficacy is observed at much lower doses than safety signals.
 - Hence, our knowledge of the benefit-risk relationship is always asymmetric (*Drug Information Journal: 2008; 45; 235-245*) :
 - All other things being equal, the dose selection challenge is to **find the minimum dose that will give adequate efficacy**. This is a calibration problem.
 - Doses selected in this manner for Phase III trials have a higher probability of having a better benefit-risk profile and a probability of success.
- Knowledge of the dose-exposure response (**DER**) relationship with respect to efficacy (and ideally at the individual patient level) **is key to rational dose selection.**

DER & Models

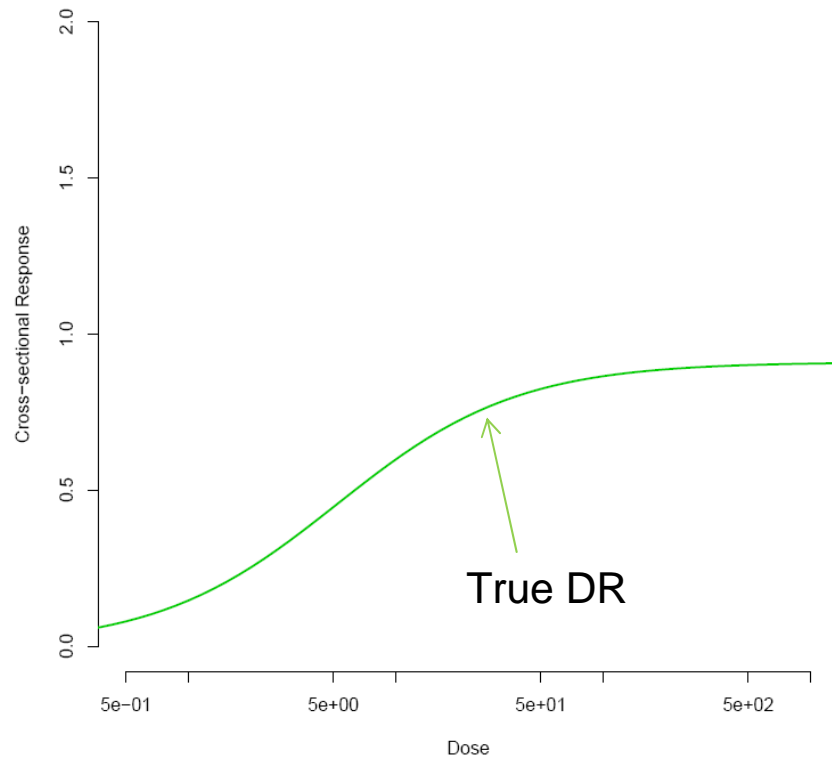
- **DER is not phenomenological.** It is driven by the underlying pharmacology that characterizes the causal chain between administration of dose and observation of response.
- Consideration of pharmacology principles represents a first step in developing a rational approach to dose response characterization. Several decades of pharmacometric research has shown that **quantitative pharmacology can be well captured in predictive DER models.**
 - Note: central to the PK/PD approach has been the individual patient in a population. In contrast, traditional statistical approaches only focus on the population level.
- Although knowledge of the underlying pharmacology may sometimes be limited, some basic principles such as the shape of the DER are often much more certain than our ability to measure the response profile precisely in reasonably sized trials.
 - **Poor precision** is often a **much greater issue** in dose response determination **than potential bias** introduced by pharmacological based assumptions about the DER.
- Appropriate characterization of DER **requires** a model based approach to ensure adequate precision for dose differentiation.

What is a DER Model?

- A DER model uses mathematical functions to characterize the longitudinal relationship between dose, exposure and response.
- It makes assumptions about the relationship between these variables that are grounded in pharmacological and statistical science.
 - Typical examples:
 - the relationship between dose and exposure is linear and exposure decays exponentially over time.
 - with increasing exposure, the response increases to a plateau, beyond which no further increase is observed: e.g. an Emax model.
 - the sources of variability can be appropriately assigned and accounted for.
 - a range candidate models can be used prospectively to account for the uncertainty in the most appropriate model.
 - the dose-exposure part may sometimes be skipped in a large patient trials by design.
 - The assumptions for any given drug are typically elucidated sequentially over the course of the development programme
- In clinical trials, the DER is usually assessed cross-sectionally at a discrete time point to give the typical dose response curve.

Dose Ranging vs. Dose Response Estimation

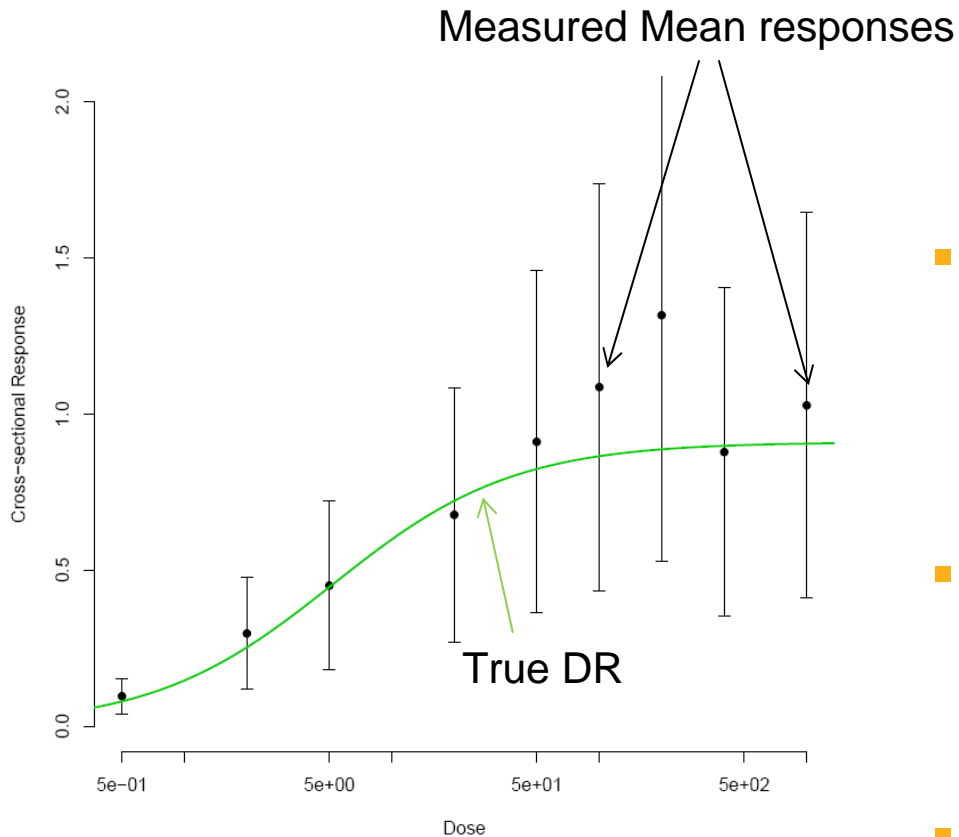
A didactic example (1/3)



- It is assumed there is an underlying true, but as yet **undetermined** average dose response relationship
- This average relationship is determined by the underlying individual patient dose response relationships which may vary considerably between patients, disease states, and time of observation.

Dose Ranging vs. Dose Response Estimation

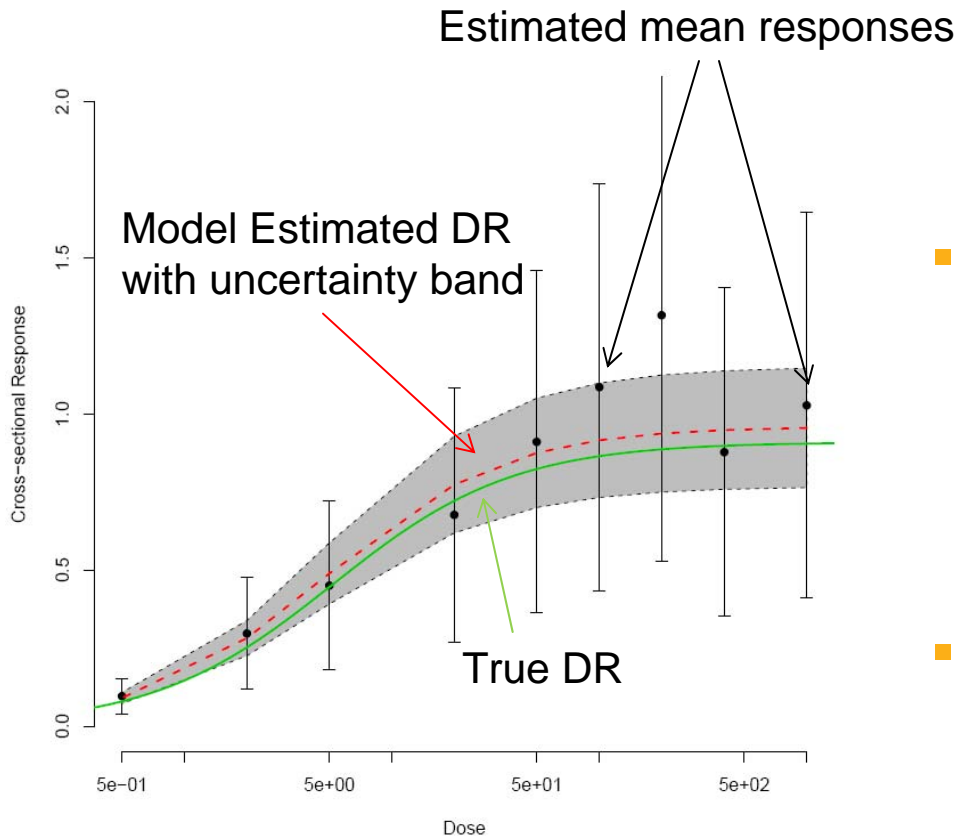
A didactic example (2/3)



- Historically, in a dose ranging trial, a range of doses is administered and the response to each treatment is analyzed independently.
- Typically the sample size is set to detect difference from placebo. Hence the precision is too poor to allow differentiation between active doses.
- A traditional dose ranging trial generally does not provide an explicit estimate of the dose response relationship.***
- Hence, it is often impossible to select the minimum dose that gives an adequate response with reasonable certainty.

Dose Ranging vs. Dose Response Estimation

A didactic example (3/3)

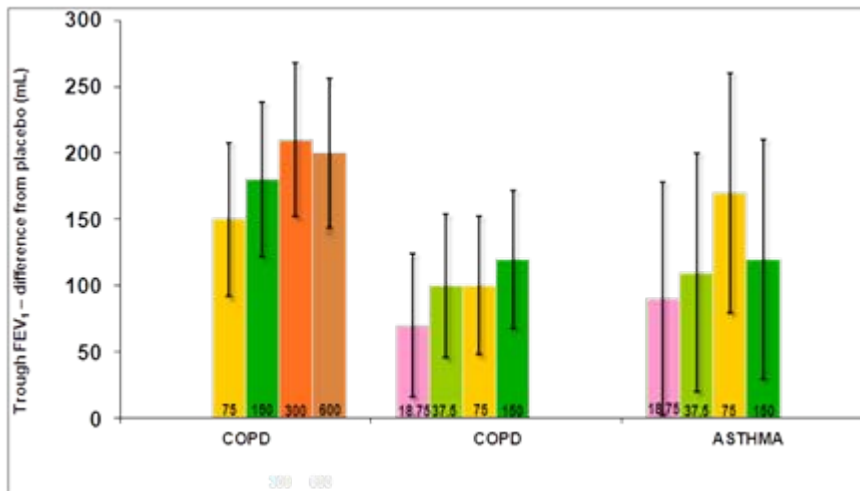


- A model-based approach explicitly postulates and estimates dose response relationship(s) though the individual measurements may be imprecise.
- A model-based approach uses the totality of the data to predict the response at any given dose level.
 - Depending on study design, model based methods can easily be extended to providing predictions at both the individual patient and population level
- This approach is akin to a calibration of the response and provides a robust basis to support the ultimate dose selection decisions.

Dose-Ranging Without Explicit DR Assessment

Does it Happen in Reality?

3 traditional dose-ranging trials in a bronchodilator development programme



- All trials met the “primary endpoint” of differentiation from placebo: i.e. the drug clearly works.
- None of the trials were able to effectively differentiate active doses due to lack of precision of the traditional approach.
- The traditional approach advocated by a health authority meant that the trials could not definitively answer the key question they had raised about dose differentiation: as designed, the trials could never achieved this objective.
- The observed large “treatment by trial” variability in this example further suggests that in some cases it will be necessary to use model-based methods to appropriately pool information across trials to obtain a robust estimate of the underlying true dose response
 - In other words, in some cases it will be necessary to look beyond the current paradigm of the independent trial as the unit for consideration

Question 1

- When should M&S be the primary analysis to establish the doses for phase 2/3 rather than traditional statistical analysis?
 - In order to estimate a dose response relationship, a model based approach is necessary.
 - It should be done in all circumstances where it is feasible.

Question 2

- How should prior knowledge be used to establish the doses for phase 2/3?
 - Prior information should always be used to underwrite the design and analysis of dose ranging activities to inform:
 - Analysis approach to **estimate** the dose response relationship.
 - Duration, intensity and sequence of treatments.
 - Number, timing and frequency of assessments.
 - Relationship of biomarkers or surrogates to clinical endpoints.
 - Patient population and sample size.
 - The **more prior knowledge** that can be built into the DR assessment, the **higher the likelihood of successful dose selection** for future trials and ultimate clinical use.

Question 3

- What information is ideally required to support a model based approach?
 - An explicit analysis plan. This may include:
 - Prospective simulation studies which test the sensitivity of model-based approaches to foreseeable assumptions and design constraints.
 - Pre-specified, but retrospective sensitivity analyses to qualify the model based predictions.
 - Ultimately, the model based predictions can be validated using data from future trials.

The Payback

Result of a systematic implementation of model-based DR assessment at a Pharmaceutical Company

Indication	Approach	Efficiencies vs Traditional design alternative
Thrombo-embolism	Omit PIIa, Model based D/R, adaptive design	2750 pts, 1 year
Hot flashes	Model based D/R	1000 pts
Fibromyalgia	Prior data supplementation, Model based D/R, sequential design	760 pts, 1 year
Type II diabetes	Prior data supplementation, Model based D/R	120 pts, 1 year
Gastro-esoph. reflux	Model based D/R	1025 pts
Rheumatoid arthritis	Model based D/R	437 pts
Global anxiety disorder	Omit Ph IIb	260 pts, 1 year
Lower Urinary Tract Symptoms	Meta-analysis	Increase prob success
Urinary incontinence	Meta-analysis	Increase prob success

- Impact of dose selection strategies used in phase II on the probability of success in phase III. *Stat Biopharm Res; 2010; 2; 469-486*

- *The use of a **traditional approach** to dose selection followed by bringing a single dose forward to PIII is associated with a **low probability of success**.*
- *The probability of success is increased when more than one dose is studied in PIII*
- *The probability of success is further improved when these doses are selected using model-based adaptive designs.*

The Challenge

- It is proposed that the only rational and efficient way to explicitly assess the dose response relationship in most drug development programmes is through use of model-based methods.
- However, the lack of know-how and the specter of ***perceived*** lack of regulatory acceptance of model-based approaches still weighs heavily in many companies.
- The result is that many development programmes do not have an explicit estimation of the dose response relationship at either the individual patient or population level. As a result, dose finding activities are often sub-optimal.
- To promote and assist the use of model-based dose response assessment as an essential part of the dose selection process, clear regulatory endorsement, recommendations and ultimately guidelines are required.