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Early understanding of PK/PD: setting up success in development?

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Maximising your value through the integrated application of **Pharmaceutical Development** and **Clinical Pharmacology** expertise. \





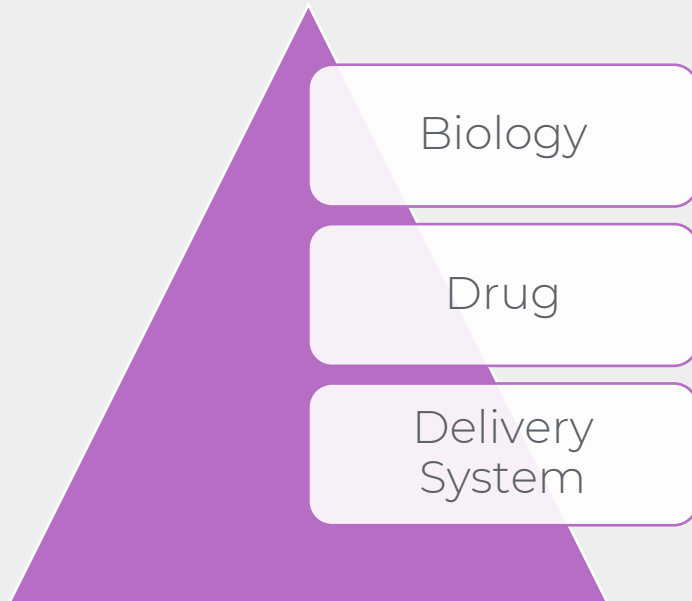
Product Design

Start with the end in mind. \

Early understanding of PK/PD: setting up success in development?

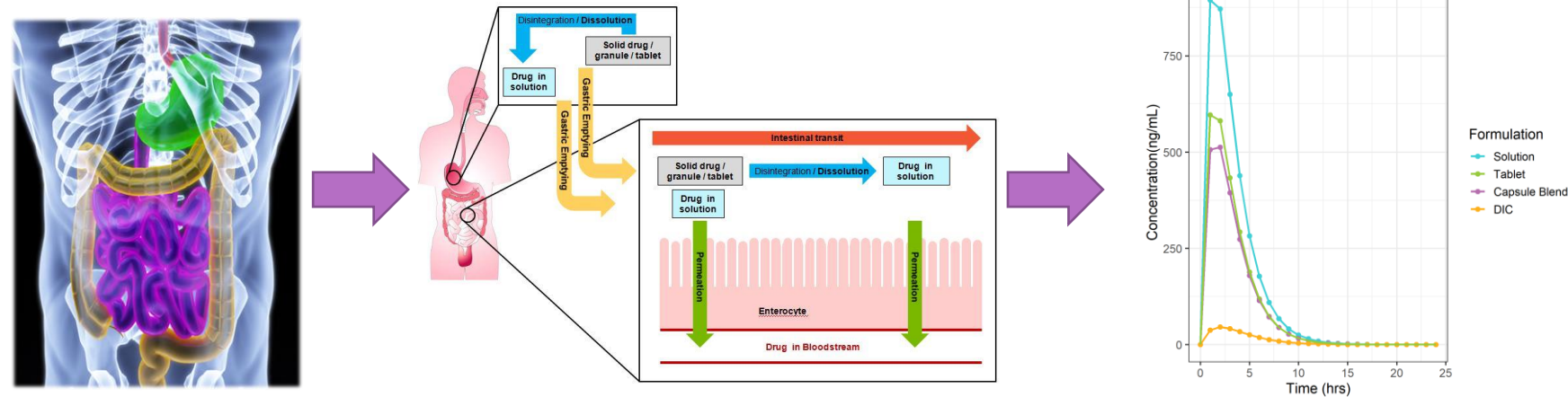
The Drug Delivery Challenge \

- Methods and approaches for delivering drugs to achieve desired therapeutic outcomes – accounting for disease biology, physicochemical properties of therapeutic entities, physiology and anatomy of route of administration



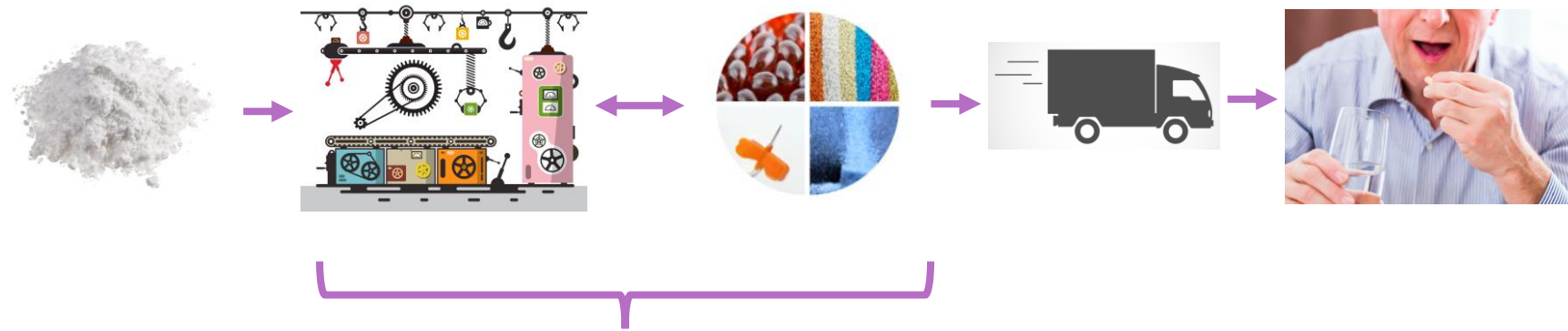
Biopharmaceutics

- **Biopharmaceutics:** the study of how the physicochemical properties of drugs, dosage forms and routes of administration affect the rate and extent of the drug absorption
- How does this relate to exposure?

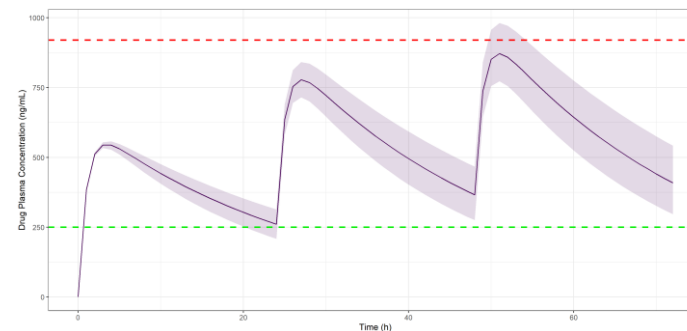


Choosing the formulation

- Understand how the formulation relates to exposure
- Then, we need exposure that will give efficacy and safety
- We need to be able to give the patient something to take!



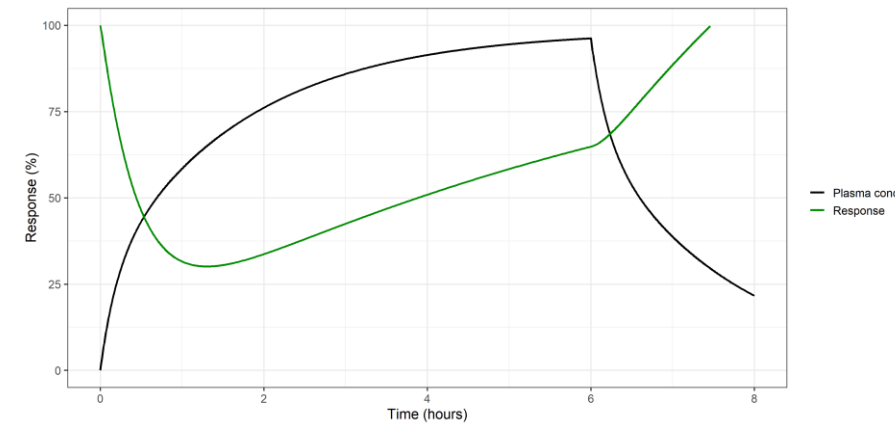
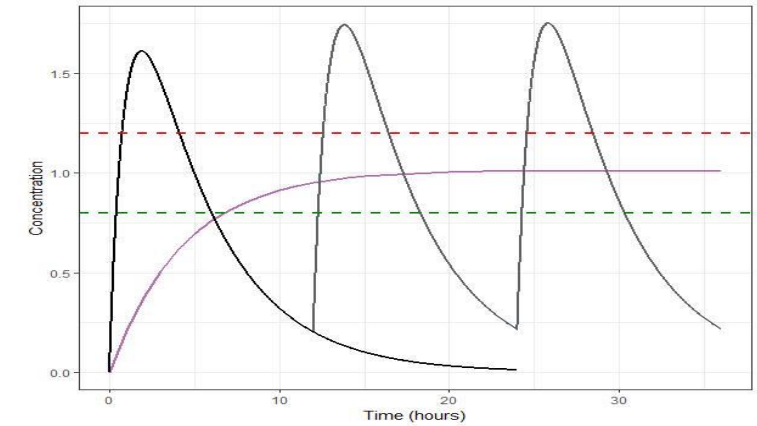
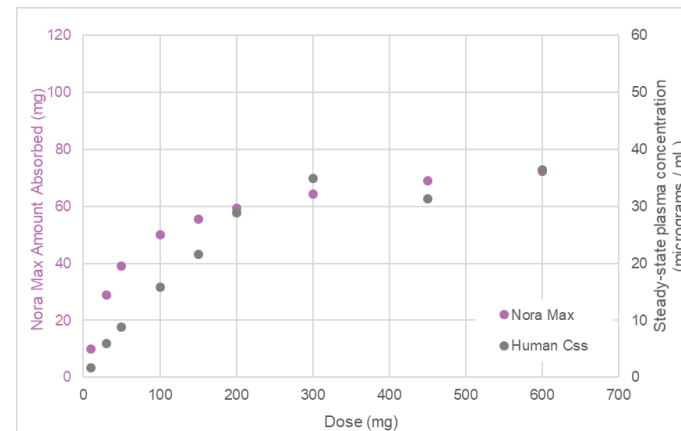
- What the patient wants,
- is willing to take
 - is easy to take and available when needed



Safety and efficacy

Data modelling to integrate data and mitigate risk

- Impact of drug properties on drug absorption
- Relationship between dose, exposure and biological effects
- Maximises the chance of success in the clinic



Clinical translation

- As we have come out of discovery and in to the pre-clinical setting an understanding of exposure-response has been developed
- Experimental data and modelling should be integrated to de-risk the compound during pre-clinical testing
 - Confirms the correct hypothesis is being prosecuted
 - Provides understanding of a safe and efficacious dose in humans
 - Informs selection of a lead formulation
- In most therapeutic areas translational modelling and Phase II studies used to optimize dose
- However, this hasn't always been the case in oncology

FDA's Project Optimus

- For Oncology dose finding studies, the aim was to find the Maximum Tolerable Dose (MTD)
- The FDA's Oncology Centre of Excellence is launching Project Optimus, a new guidance on dose optimisation for Oncology therapeutics
- Phase I: Determine range of doses to take into Randomized Phase II trial(s)
 - PK modelling and analysis of PD biomarkers to help enable
- Phase II: Determination of optimum dose with PopPK modelling to assess efficacy and tox relationships

Table 1. Dose interruptions and reductions in initial registration trials for small-molecule KIs approved for oncology indications with PMC or PMR to study alternate doses (percentage of patients on registration studies)

Drug	Dose interruption	Dose reduction	Dose interruption or delay
Erlotinib	62%	19%	NA
Vandetanib	47%	49%	80%
Cabozantinib	NA	79%	86%
Ponatinib	66%	52%	74%
Ceritinib	69%	59%	71%
Idelalisib	NA	34%	53%
Lenvatinib	56%	68%	90%

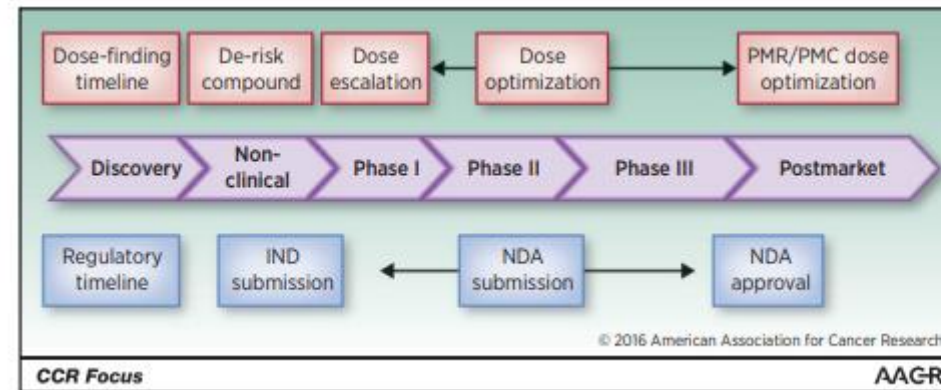


Figure 1. In the current oncology drug development era, regulatory submission of a marketing application may occur as early as phase I development. However, dose optimization frequently has not been completed at this early stage and may continue into the postmarket setting. IND, Investigational New Drug; NDA, New Drug Application.

P.A. Janne et al 2016

FDA's Project Optimus - Sotorasib

- FDA's Project Optimus now coming in to effect
- Amgen's Sotorasib is an approved KRAS G12C inhibitor
- FDA required Amgen conduct a randomized clinical trial comparing labelled dosage (960 mg daily) to a lower dose (240 mg daily)
- Similar clinical exposure levels and patient response had been shown for patients in registration trial and those who received the lower dose

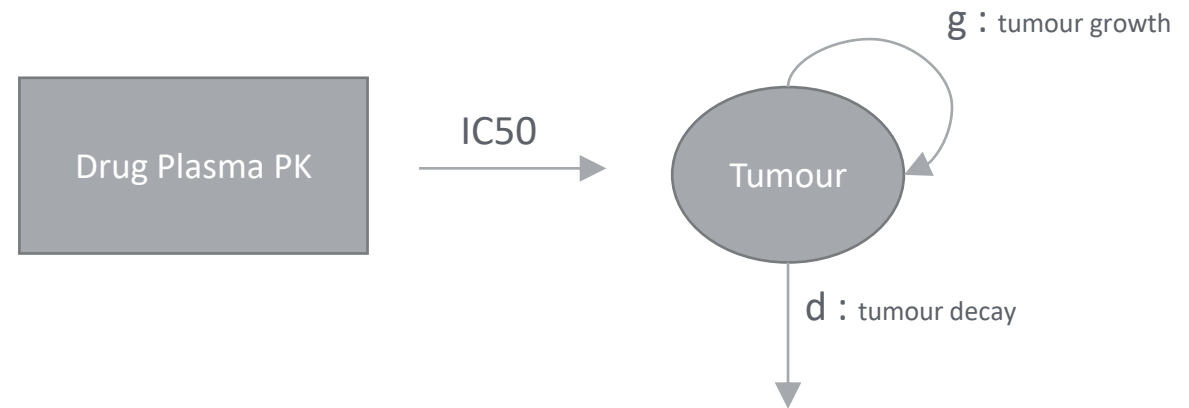
“This isn't just an Amgen issue – this is a **cultural issue** throughout oncology”

Harpreet Singh, MD, director of FDA's Division of Oncology

Clinical translation modelling

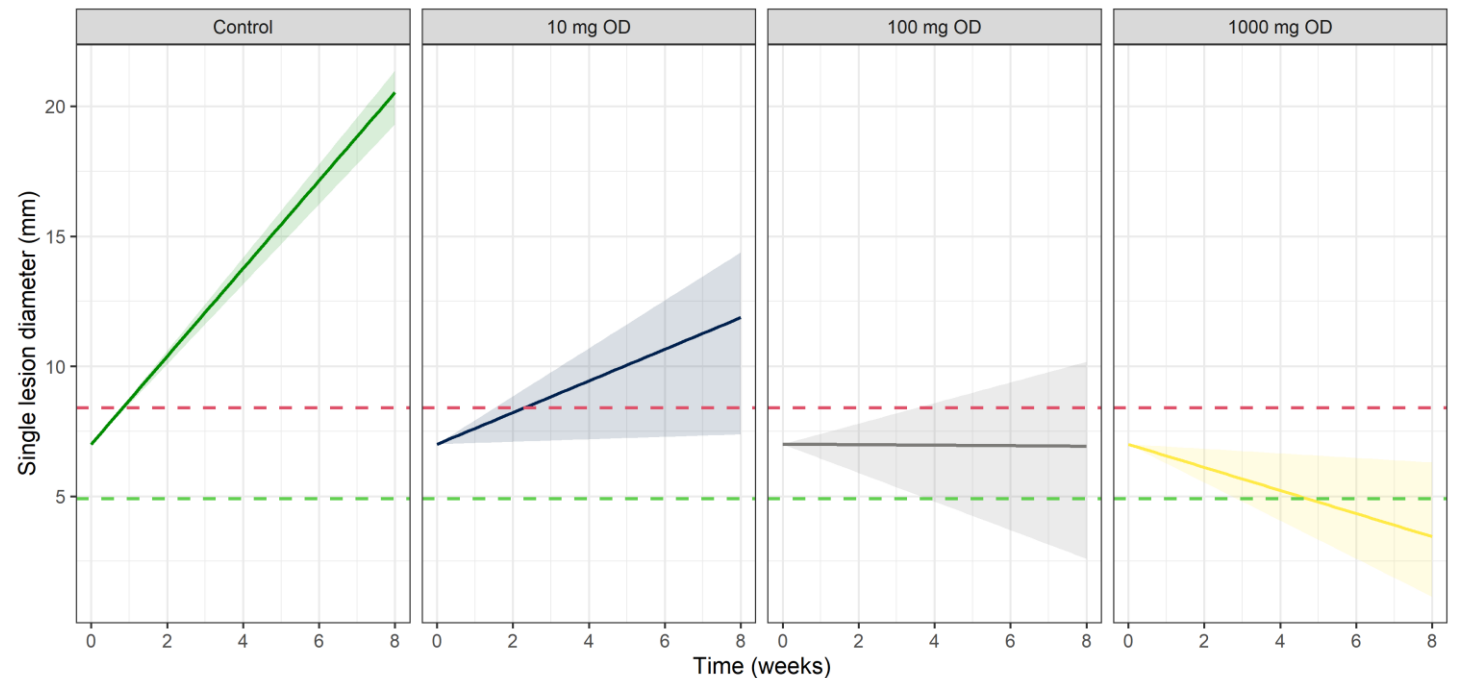
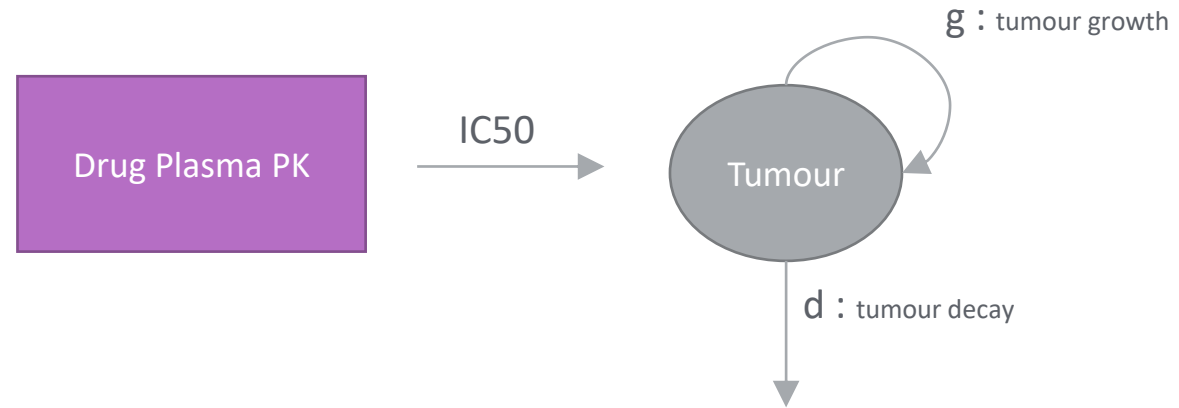
- A PK-PD-TGI model has been established on mouse xenograft data
- The established model describes the relationship between exposure-pharmacodynamics, and anti-tumour effect in mice
- How can this be translated to humans?

$$\frac{dR}{dt} = g - d * \frac{[Drug]^h}{IC50^h + [Drug]^h}$$



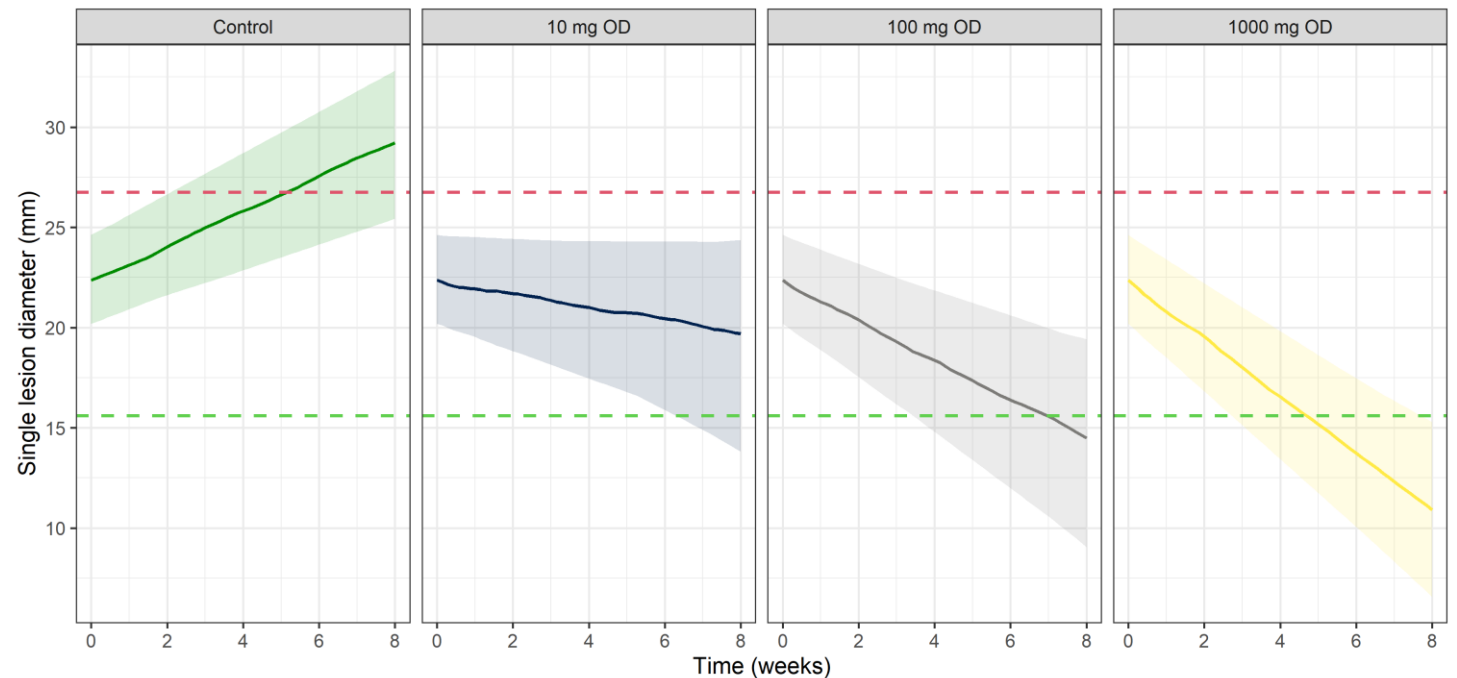
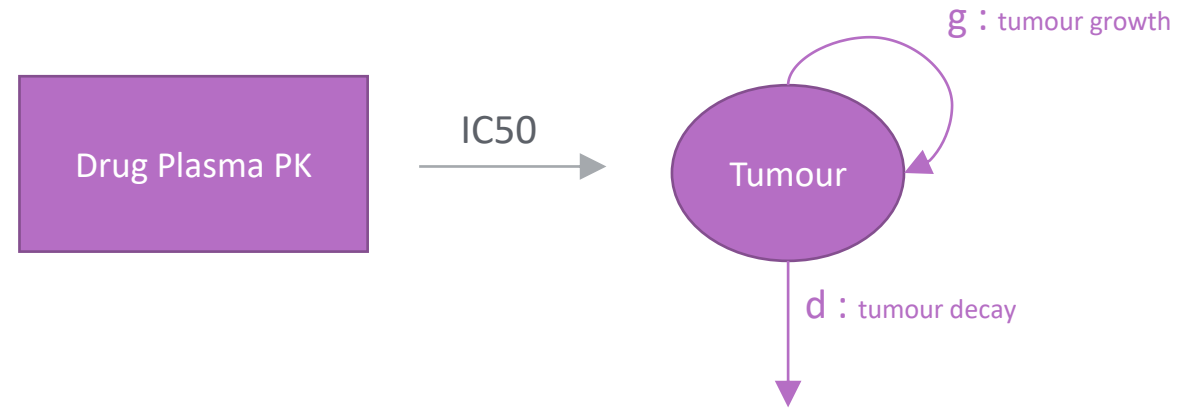
Clinical translation modelling

- PK profile / half-life in preclinical species can be very different to human PK profile
- Human PK model substituted for mouse PK model
- Assumed that relationship between free drug concentration and anti-tumour effect is constant across species
- Informs optimum dose (and potentially input profile)



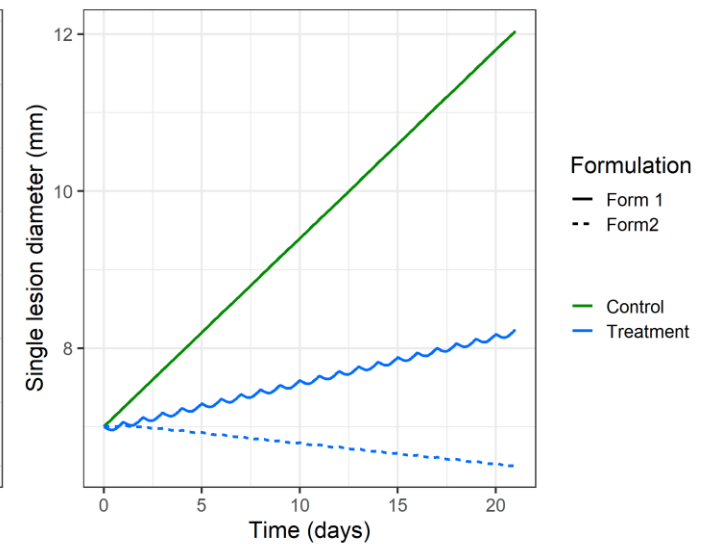
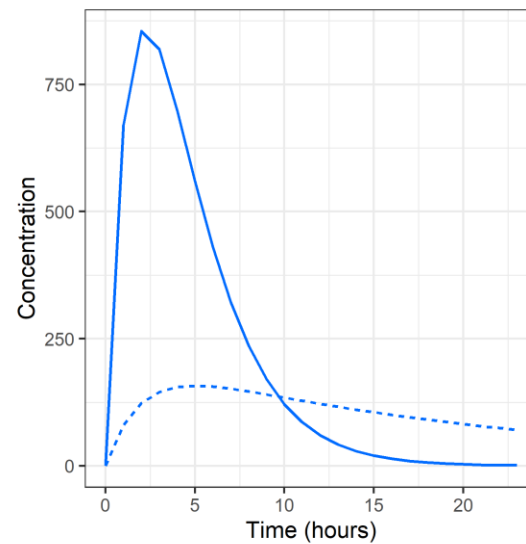
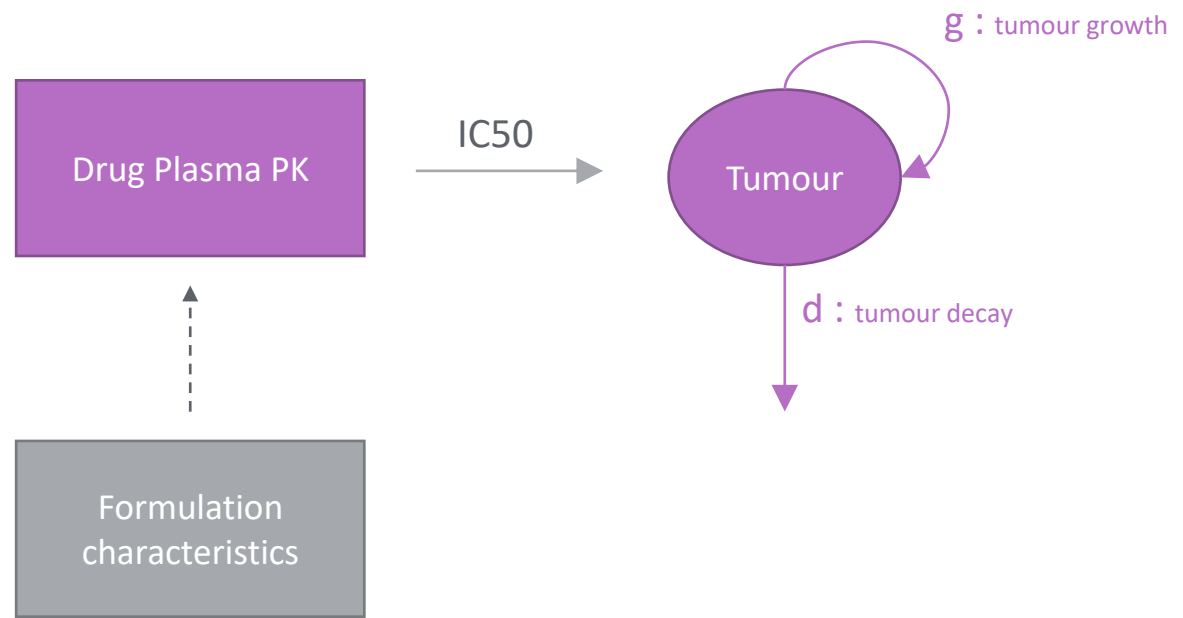
Clinical translation modelling

- Tumour growth kinetics do differ from xenograft mice to humans
 - Clinical tumour growth rates slower
- Derive tumour growth kinetics from clinical data which is relevant to the compound of interest
- Clinical anti-tumour effect simulated,
- Categorised using RECIST criteria



Clinical translation modelling

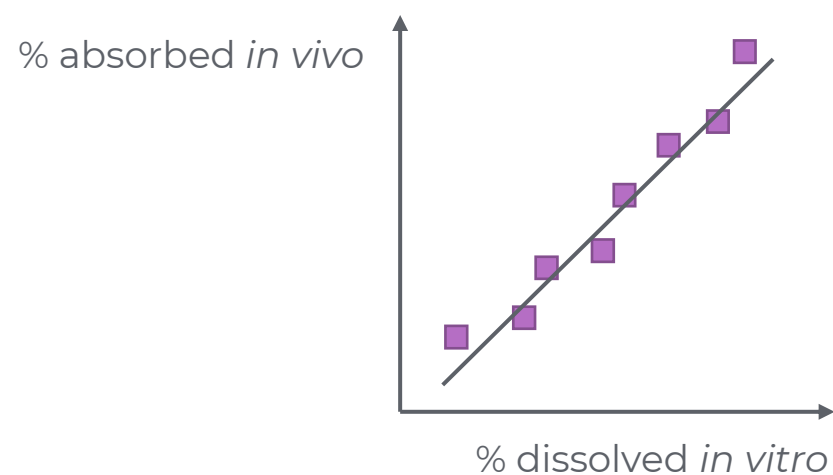
- If we had previously modelled different formulations we could then predict which formulation is mostly likely to give us the desired PK/PD
- Perform simulations for each formulation
- Select best forward to take forward



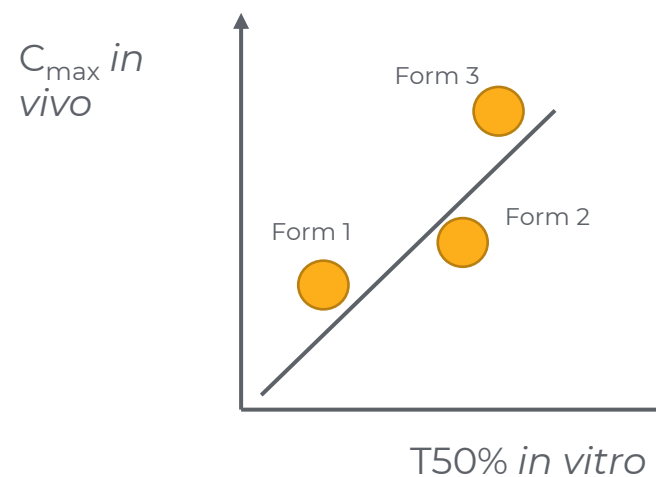
IVIVC

- IVIVC links *in vitro* performance to *in vivo* performance

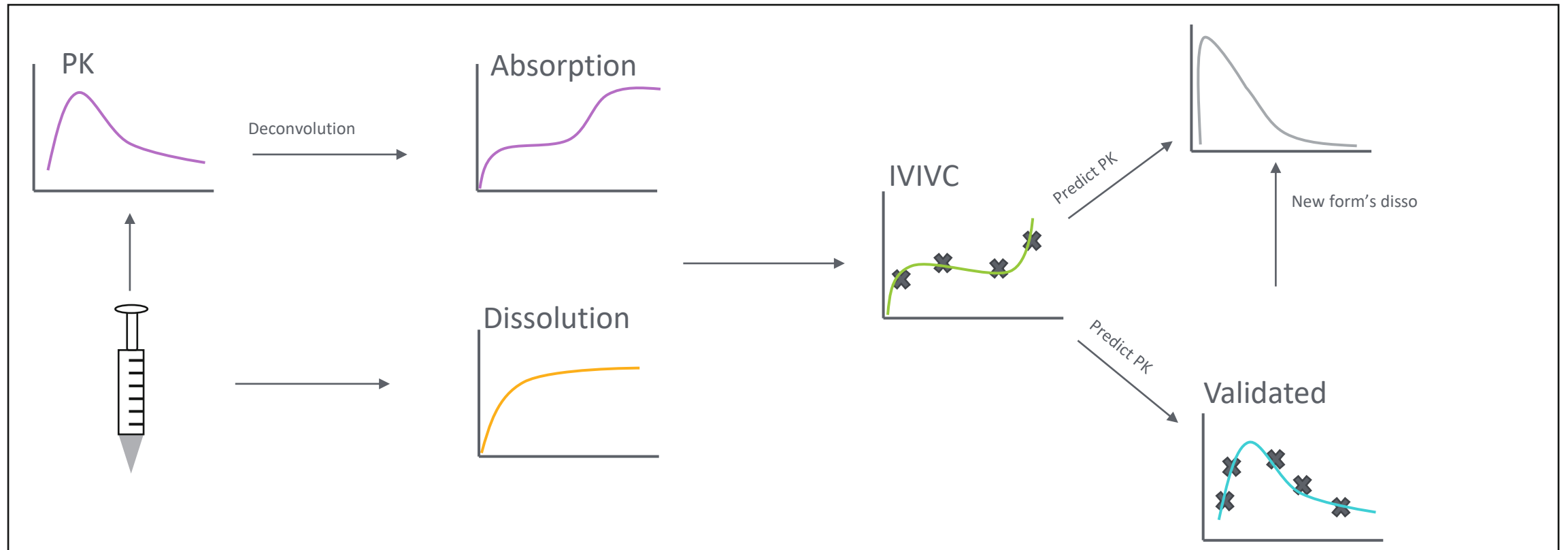
Level A (most powerful)



Level C (less informative)



Key steps for performing IVIVC



Benefits of IVIVC

Successfully establishing an IVIVC can:

- Waive requirement to show evidence for bioavailability or bioequivalence
- Allow more focus to be spent on formulation work, as opposed to in vivo studies, thus less time and money spent testing in animals and humans





Thank you for listening! Any questions?

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