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Designing and delivering an early development clinical programme

Peter Scholes, CSO, Quotient Sciences

Insights into Medicine Developability

6th November 2020

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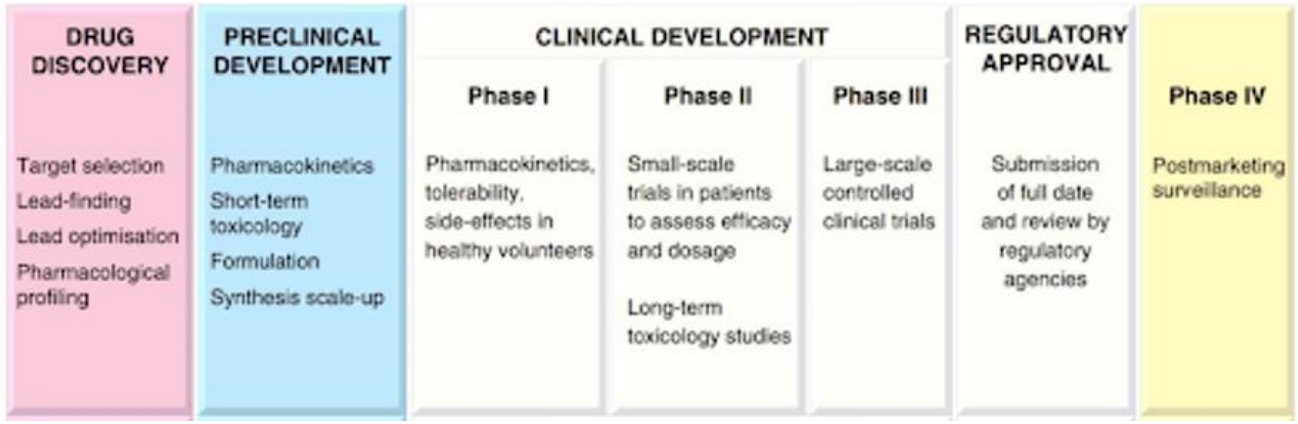
Overview

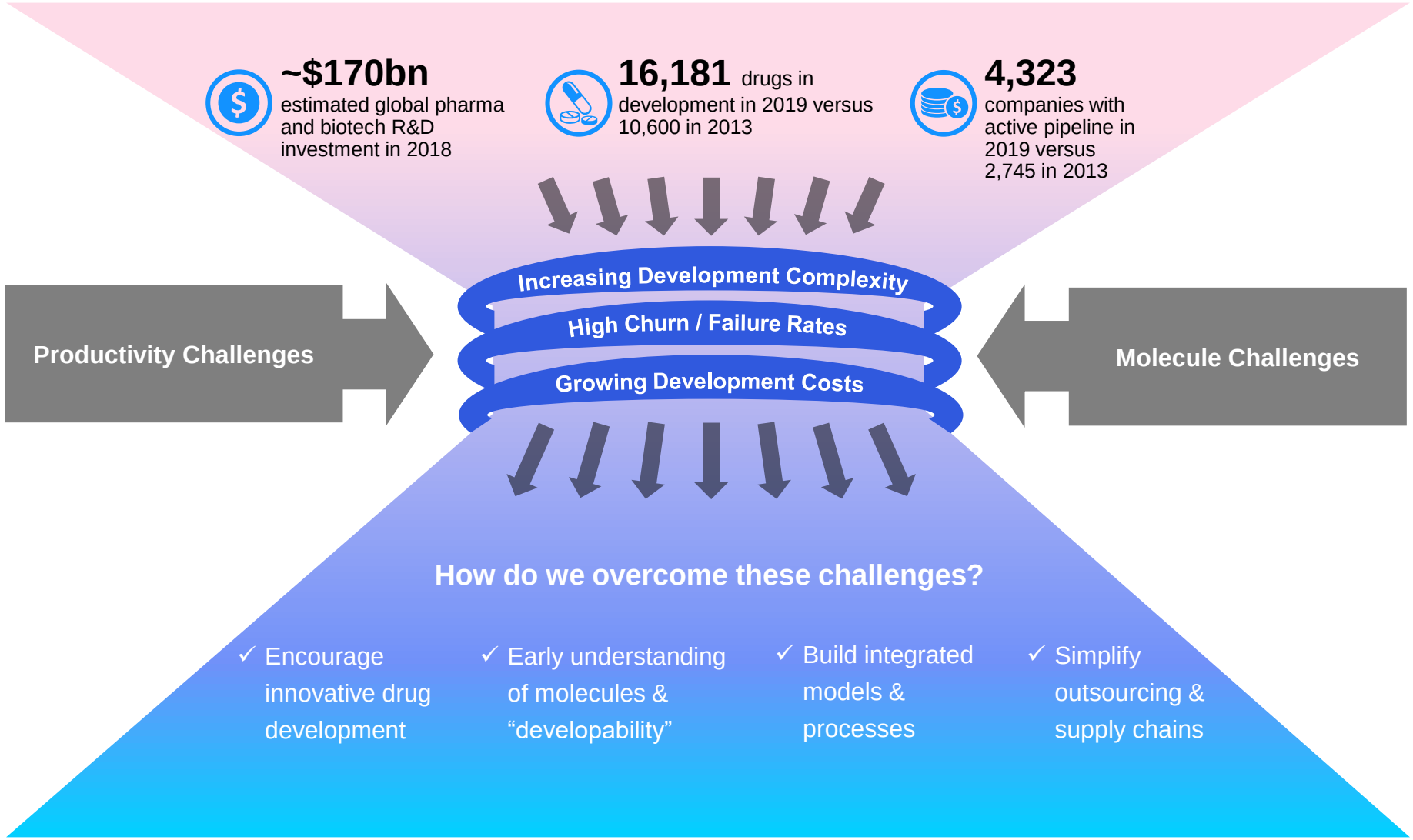
- Fundamentals of early clinical research…and the importance of the product
- First in human (FIH) studies – design and principles
- Integrated programs to accelerate Proof-of-Concept (POC)
- Optimising drug products and drug delivery post FIH
- Case studies
- Regulatory and ethics framework for early clinical research
- Summary

Classic phases of clinical development

- **Phase 1 (small numbers, healthy volunteers)**
  - Is the drug safe and tolerated?
  - PK (what does the body do to the drug?)
  - PD (the effects of the drug on the body?)
  - Early proof of pharmacology and mechanism?
- **Phase 2 (low hundreds, patients)**
  - Is the drug safe?
  - Efficacy (Does it work - exploratory)
- **Phase 3 (high hundreds, patients)**
  - Is the drug safe?
  - Efficacy (Confirm it works)
- **Post licence (Phase 4)**
  - Pharmacovigilance – Is the drug safe?

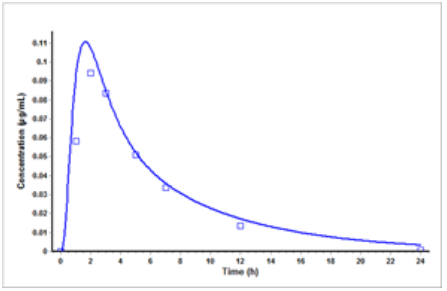


Development cost and complexity continues to increase



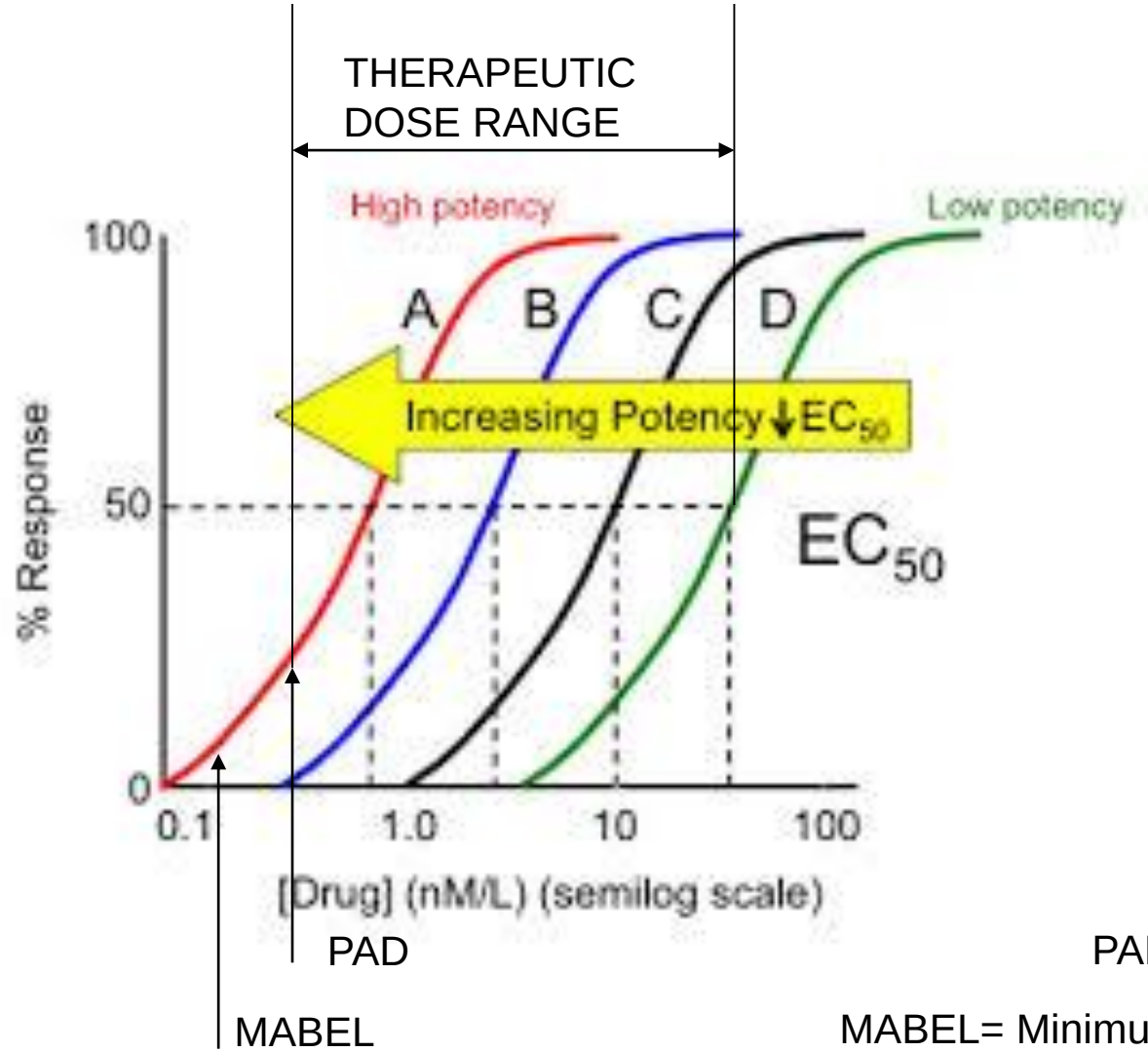
PK and PD responses are required for success

- **Pharmacokinetic (PK) response**
  - What the body does to the drug
  - The mathematical description of the time course of the processes of Absorption, Distribution, Metabolism and Excretion of drugs (ADME)



- **Pharmacodynamic (PD) response**
  - What the drug and/or its metabolite(s) do to the body
  - Pharmacological actions of a drug within the body
  - Influenced by drug concentration at receptor not dose
  - *Desired - therapeutic or beneficial response*
  - *Undesired - adverse or toxicological response*

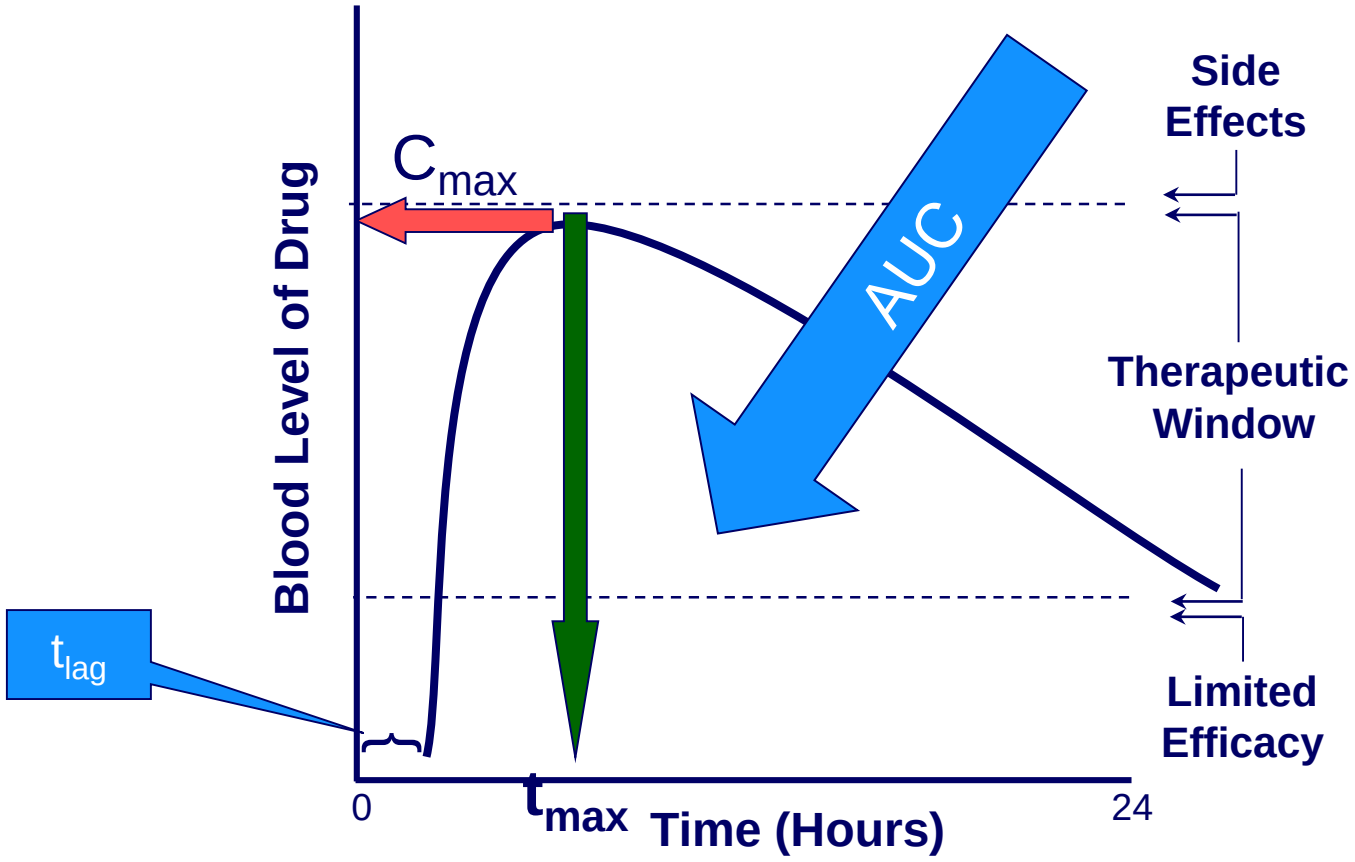
Pharmacodynamics (PD) – dose response curve



PAD = Pharmacologically Active Dose

MABEL= Minimum Anticipated Biological Effect Level

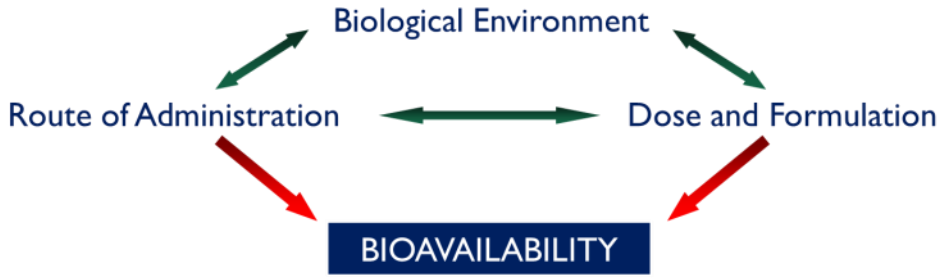
Pharmacokinetics (PK) – exposure curve



- Need to get enough drug exposure to have therapeutic effect
- Too little exposure – drug doesn't work
- Too much exposure – drug can cause side effects
- Duration of action important for how many times a day you take the drug

Biopharmaceutics and bioavailability

- **Biopharmaceutics**
  - The relationships between the formulation of the drug, the route of administration and the physiological/biochemical environment within the body



- **Bioavailability (F)**
  - The *rate* and *extent* at which the drug reaches the systemic circulation (plasma/blood) from the site of administration
  - A relative term, comparing at least two administrations:
    - Frel - compares two extravascular doses/routes
    - F - compares extravascular dose to iv dose

Absorption and bioavailability - one simple equation

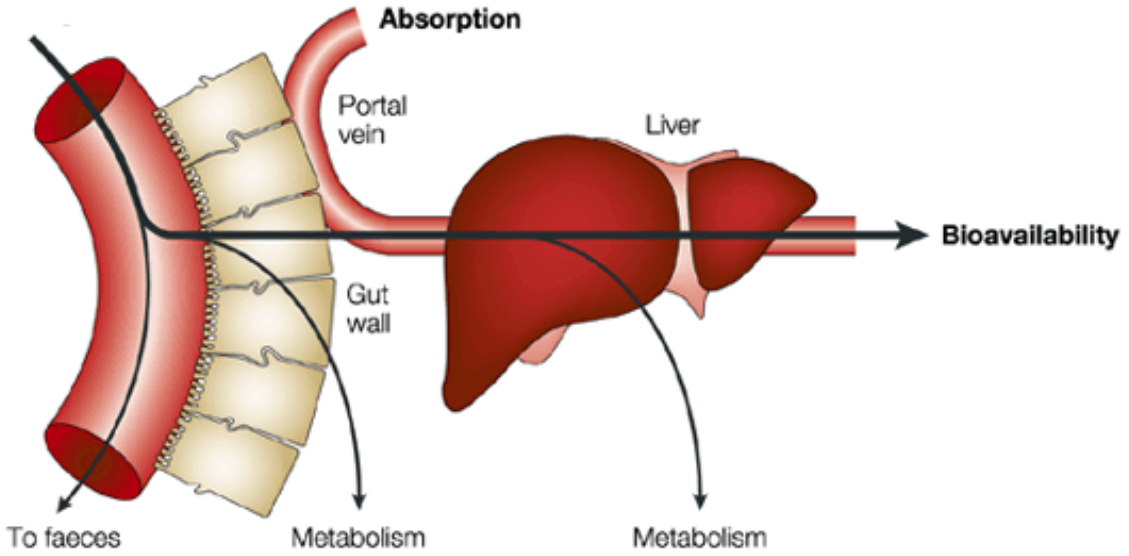
- **Bioavailability (F) in the systemic circulation is influenced by**
  - Amount of drug absorbed from the GI lumen
  - Amount surviving pre-systemic metabolism

- **F = Fabs x Fg x Fh**

input

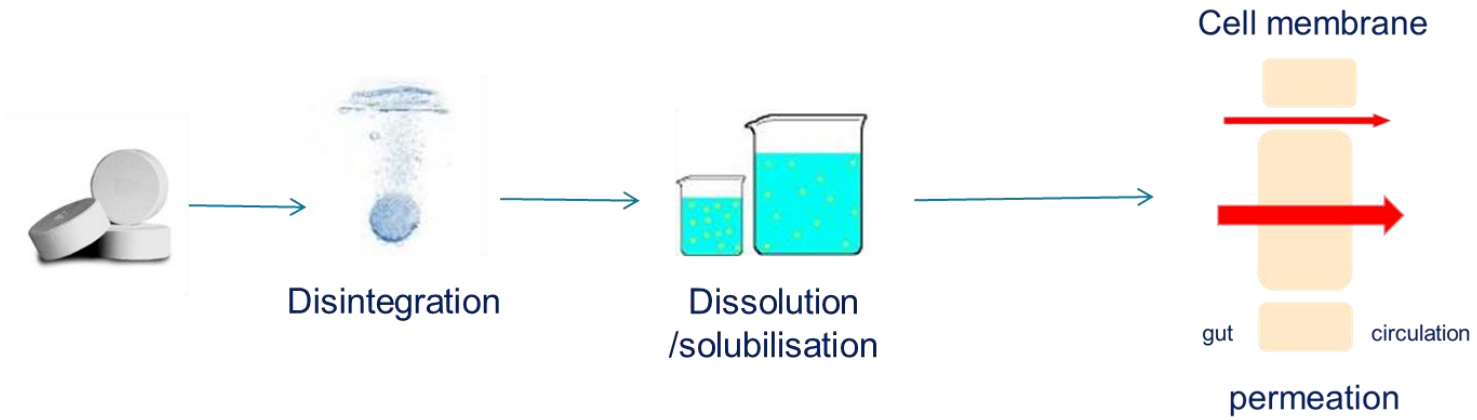
output

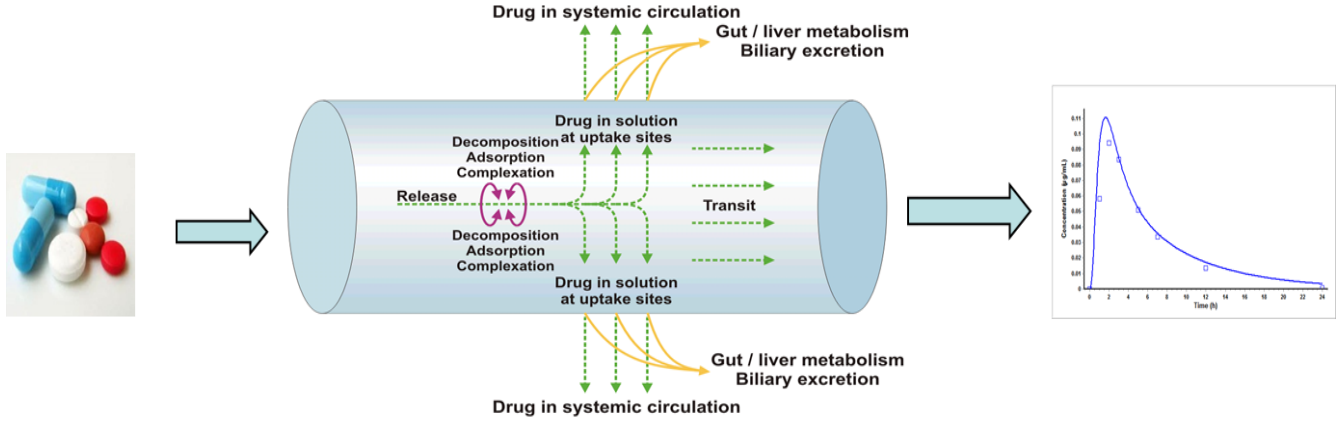
F = bioavailability (ie rate & extent of drug reaching systemic circulation)
Fabs = fraction absorbed (ie drug entering epithelial cell membrane)
Fg = fraction surviving first pass gut metabolism
Fh = fraction surviving first pass hepatic metabolism



Nature Reviews | Drug Discovery

Drug delivery challenges for oral products….



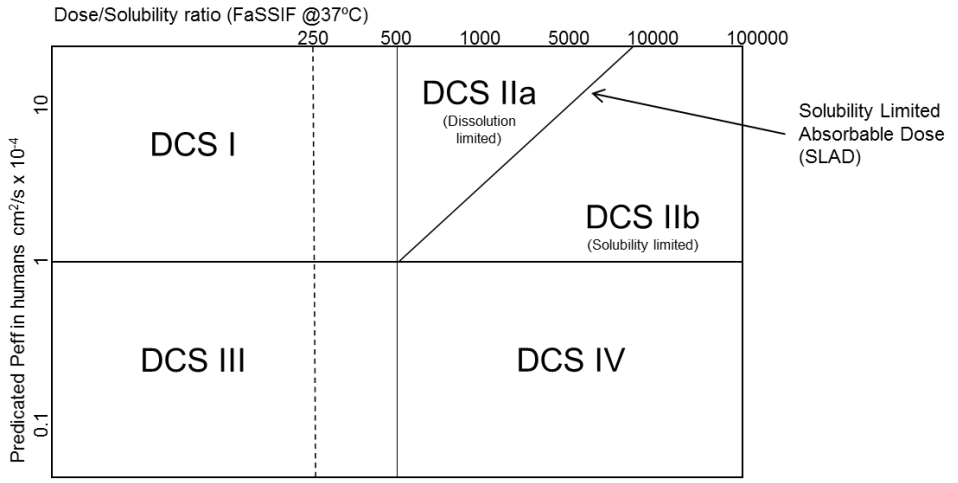


(Dressman et al., Pharm. Res. 15: 11-22, 1998)

Biopharmaceutics Classification System (BCS) / Developability Classification System (DCS)

- **BCS – *Amidon et al., 1995***
  - Regulatory framework designed to allow sponsors to apply for biowaivers for clinical BE studies for certain types of compound
  - Classification system based on API solubility and permeability and dosage form dissolution
- **DCS – *Butler and Dressman, 2010***
  - Considers intestinal solubility in FaSSIF and compensatory small intestinal permeability
  - DCS IIa & IIb classification to direct formulation strategies
  - Greater focus on developability and in vivo performance prediction
- **rDCS – Rosenberger, *Butler and Dressman, 2018***
  - Provides standard sets of compounds or markers
  - Allows tier 2 investigations based on certain drug properties
- **Industry challenge: >70% NCEs are Class II**

BCS I Good solubility Good permeability	**BCS II** Poor solubility Good permeability
BCS III Good solubility Poor permeability	**BCS IV** Poor solubility Poor permeability



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First-in-Human (FIH) Studies

(Very) rare incidents during FIH trials….


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Six men in intensive care aft
goes wrong

· Volunteers were testing treatment for arthritis
· US company says adverse reaction is 'extremely rare'

Six men were in intensive care in a north London hospita
pharmaceutical company's trial went wrong. Regulatory
suspended the drug trial and are investigating in collabor
The six were healthy volunteers, paid to take part in the e
testing of a potential new medicine for inflammatory dise
arthritis and leukaemia. The volunteers were needed to e
were any side effects or obvious problems with the drug
people who have the conditions.

But on Monday, the first day of the trial, the Medicines ar
Regulatory Authority (MHRA) said yesterday all six men
commercially run clinical trials unit at Northwick Park ho
the men reportedly had extreme breathing difficulties wi
taking the drug and his family was told his legs had turne
the Sun newspaper.

TeGenero incident 2006

EXPERT SCIENTIFIC GROUP ON

PHASE ONE CLINICAL TRIALS

FINAL REPORT

3Oth November 2006

Duff Report 2006


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Man dies after being left brain-de
serious side effects during a dru
France

· Five other volunteers were also hospitalised after taking
· Three of the men are suffering from a 'handicap that cou
· Was described as 'an accident of exceptional gravity...w
· The trial was run by private lab Biotrial for pharmaceutic

By IMOGEN CALDERWOOD FOR MAILONLINE

PUBLISHED: 18:13, 17 January 2016 | UPDATED: 01:05, 18 January 2016

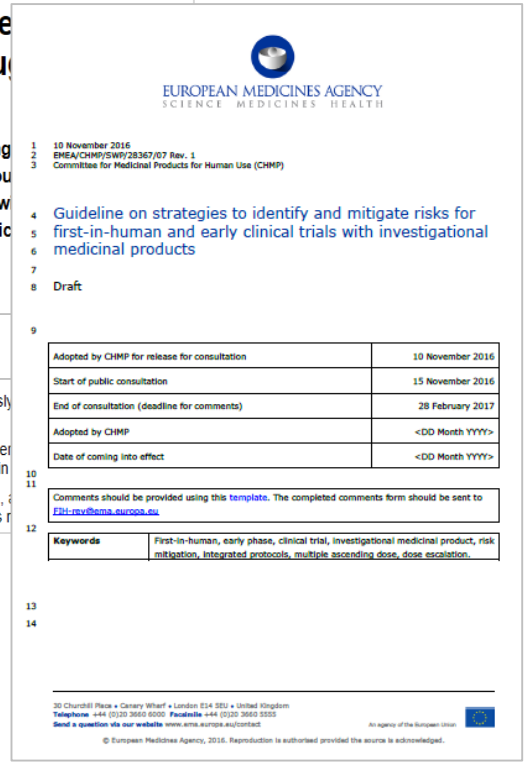
Share 435 shares

A man who was left brain-dead after a drugs trial in France went seriously
according to the hospital which had been treating him.

Five other volunteers were also hospitalised after taking the trial painkiller
a stable condition', according to the statement released by the hospital in

But three of the men are suffering a 'handicap that could be irreversible',
Edan, the head of the hospital's neurology department, and another has

Biotrial incident 2016


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Draft

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	<DD Month YYYY>
Date of coming into effect	<DD Month YYYY>

Comments should be provided using this template. The completed comments form should be sent to FIH-rev@ema.europa.eu

Keywords	First-in-human, early phase, clinical trial, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
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http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500216158&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Bial - Catalyst for Revised EU FIH Guideline - July 2017

- **'Guideline on strategies to identify and mitigate risks for FIH and early clinical trials with IMPs products'** http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232186.pdf
- **Primary purpose: minimise subject risk in early trials with both small molecule and biological IMPs**
- **Takes on a wider scope and also considers the transition of single / multiple doses to other components of multi–part protocols e.g. Food Effect / Drug Drug Interaction / Patients**
- **Main change is requirement that dose ranging should not exceed the anticipated therapeutic dose range….. unless scientifically justified.**
- **No longer ethical to identify the Maximum Tolerated Dose (MTD) in healthy subjects.**
- **No significant changes to preclinical toxicology requirements but there should now be a greater emphasis on defining the dose response curve and pharmacology (*in vitro* and *in vivo*)**
- **2005 FDA FIH guideline which considers NOAEL (toxicology) and PAD also still relevant** https://www.fda.gov/downloads/drugs/guidances/ucm078932.pdf

NOAEL = no observed adverse event level
PAD = pharmacologically active dose

FIH study populations

- **Phase 1 and FIH studies typically in healthy volunteers**
  - Exception FIH oncology studies and “higher risk” studies
  - No therapeutic intent (i.e. no benefit to the volunteers)
  - Risks must therefore be negligible / minimised
- **Advantages**
  - Easy to recruit – time and cost effective
  - More homogenous (e.g. no confounding co-meds or co-morbidities)
  - May tolerate study procedures better (e.g. multiple cannulation)
- **Disadvantages**
  - May not be able to obtain target related biomarker data
  - Target expression may be different in healthy volunteers when compared to patients, may affect safety profile
- **Inclusion and exclusion criteria need to be tailored for each study**
  - Older subjects - with stable background conditions and stable prescribed medication can be included on a risk assessed basis
  - WOCBP (women of child-bearing potential) – can be included on a risk assessed basis

FIH study objectives

- **Primary:**
  - To investigate the safety and tolerability of DRUGX when administered as single and multiple oral doses in healthy subjects
- **Secondary:**
  - To evaluate the pharmacokinetics of DRUGX when administered as single and multiple oral doses in healthy subjects
  - To evaluate the effect of food on the pharmacokinetics of DRUGX when administered as a single oral dose in healthy subjects
  - To explore the PD endpoints suggestive of DRUGX treatment effects

Study and protocol design considerations

- **Double-blind, placebo-controlled**
  - If no placebo then all (post dose) AEs assigned to drug
- **Cross-over (same) v parallel (separate) groups**
  - Cross-over allows subjects to act as own controls and make within subject PK and PD dose response comparisons
  - Cross-over design has risk of carry over (PD and PK) and drop out of subjects
  - Parallel-group has advantage of more subjects exposed to drug
- **Stopping criteria**
  - 1 x serious adverse event, if considered to be related to the IMP
  - 2 x severe or clinically significant Adverse Events (AEs), considered to be at least possibly IMP related

Dose selection, starting dose and maximal exposure limits

- **Based on preclinical pharmacology and safety studies in relevant species**
  - Pharmacology - *in vitro* (compare with human cell lines) and *in vivo* animal disease models
  - Safety pharmacology – vital organ systems in animals
  - General tox – selection of relevant species depends on metabolism and target expression
  - 2 species - typically rat and dog for small molecules and primates for large molecules
  - Genotox (reprotox not usually performed before Phase I)

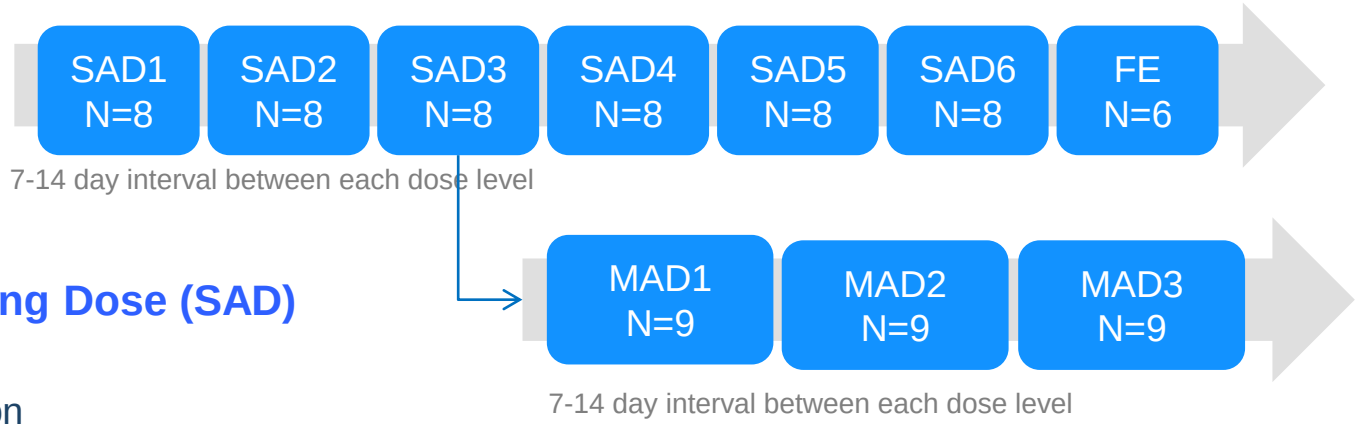
- **Calculation of dose is based on:**
  - Estimated pharmacodynamic (PD) dose range in humans
  - Generally, starting dose should be sub-pharmacological
    - MABEL - Minimum Anticipated Biological Effect Level)
  - Upper dose (exposure limit) defined as limit of estimated PD range in humans
    - NOAEL - No Observed Adverse Effect Level exposure cap in most sensitive /relevant species

Sentinel dosing, interim reviews and dose escalations

- **Sentinel groups and safety monitoring**
  - The inclusion of sentinel dosing is now standard for NCEs
  - Typically included in first 2 cohorts (dose levels)
  - Typically, 2 subjects (1a, 1p) in each cohort dosed 24h apart and safety observed by PI

- **Escalation of dose**
  - Depends on estimated shape of dose response curve in humans and potential toxicity. e.g. steep or shallow, is the estimated PD (therapeutic) dose range narrow?
  - Initial escalation should be conservative based on knowledge of the target
  - Commonly < 3x increase to ensure safe separation of dose levels
  - Guided by arising exposure (Cmax and AUC) and safety data following interim data reviews after each dose
  - Protocol written flexibly to allow optimal dose selection for next cohort.

Study design and assumptions – starting point



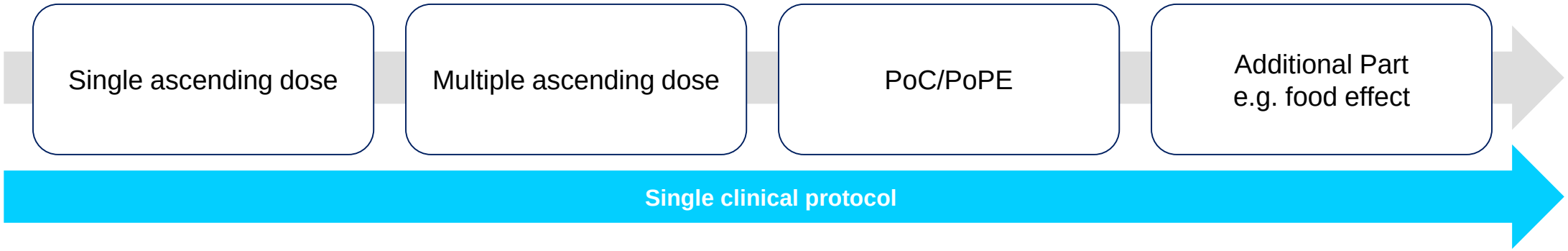
- **Single protocol, single regulatory submission**
- **Double-blind, placebo-controlled Single Ascending Dose (SAD)**
  - 6 groups of n=8 healthy subjects (6A:2P)
  - 1 group of n=6 healthy subjects (6A) – fed administration
  - Sentinel dosing at initial dose levels (until deemed not required by PI)
  - Safety and PK data required for dose escalation decisions
- **Multiple Ascending Dose (MAD) initiated when sufficient data available to support dose selection**
- **Double-blind, placebo-controlled multiple ascending dose**
  - 3 groups of n=9 healthy subjects (6A:3P)
  - QD, BID or TID dosing in fasted or fed state (if food effect data are available)
  - 7-days dosing
  - Safety and PK data required for dose escalation decisions

Data outcomes from the FIH study

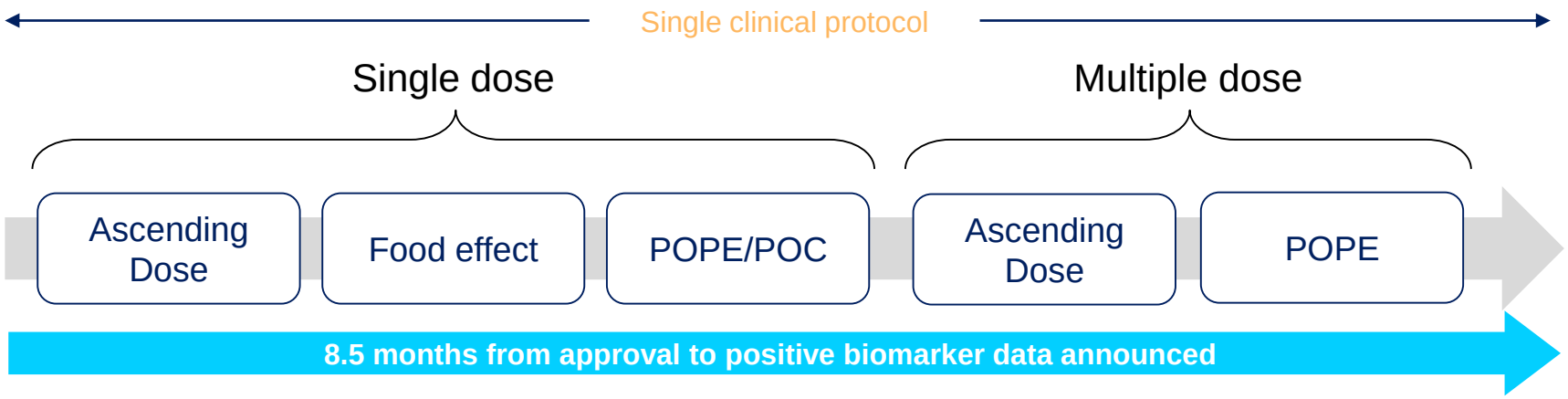
- **Arising data vital to determine if development will continue or not**
  - Unacceptable side effects or PK, absence of PD signals
- **Bad news can be good news**
  - If a drug is not going to be successful it is better to know early and quickly
- **Arising data and knowledge important**
  - Identify key issues
    - Adverse events (local, systemic….Cmax or AUC related)
    - Non-linearity (sub or supra proportional PK)
    - High PK variability within and between subjects (>30-40% CV)
    - Impact of food
    - PK-PD relationships
    - Potential for drug-drug interactions
    - Difference in sub-populations (age, gender, ethnic groups)
  - Guides the design of future studies or program termination

Evolution of First-in-Human programs

- **Early phase studies have historically been performed as separate, stand-alone protocols**
- **However, multi-part programs under a single clinical protocol are now common-place**
- **Typically, these include single ascending dose, and multiple ascending dose...plus**
  - Proof of concept or pharmacological effect - biomarkers or PD models in healthy volunteers or patients
  - Additional investigations - food interaction, gender/age/ethnic groups, drug-drug interactions, etc



Case study: Multiple objectives in an integrated protocol



POPE = Proof of Pharmacological Effect

- Corcept Therapeutics: California-based pharmaceutical company
- CORT125134, a selective glucocorticoid receptor antagonist for Cushing's Disease
- Multiple, key phase 1 objectives encompassed in a single clinical protocol
- MHRA response in 13 days, and approval in 21 days
- Positive data announced 8.5 months after regulatory approval

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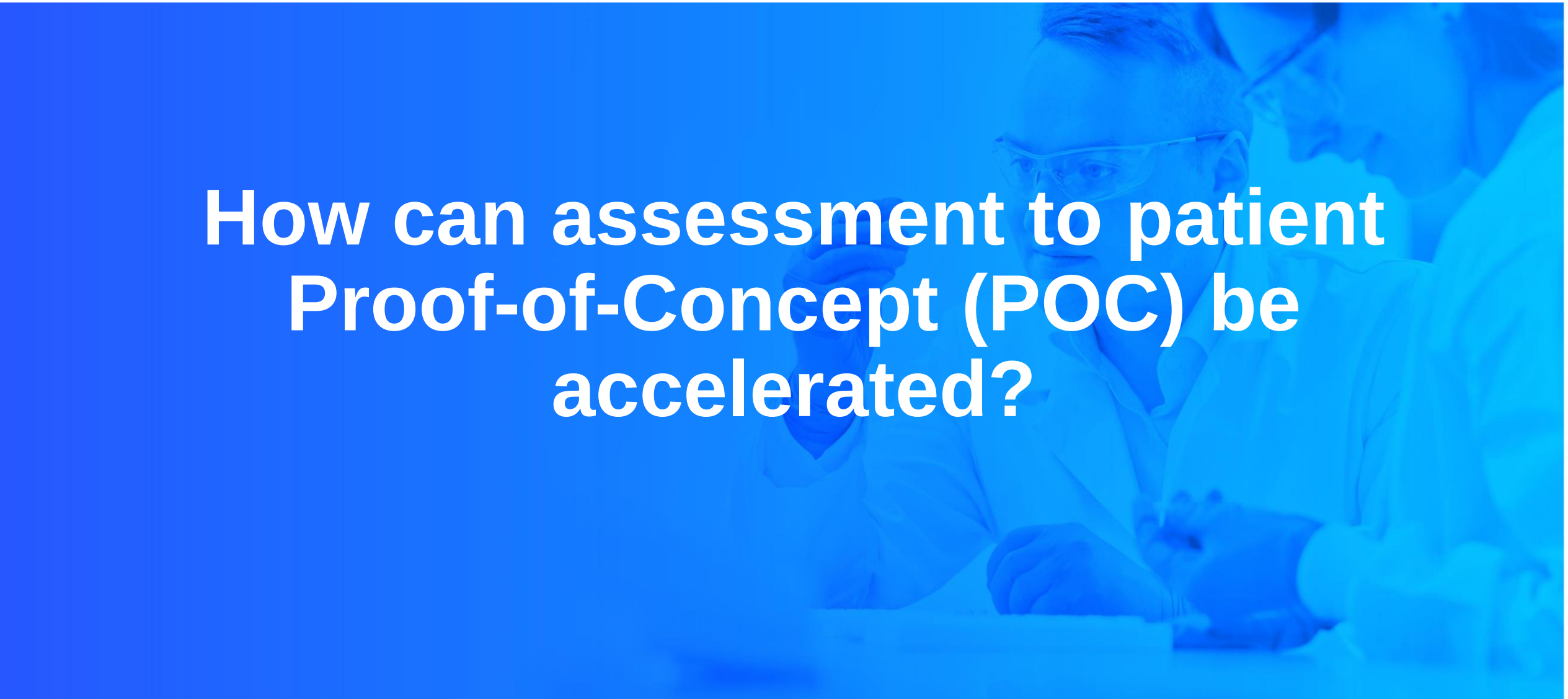
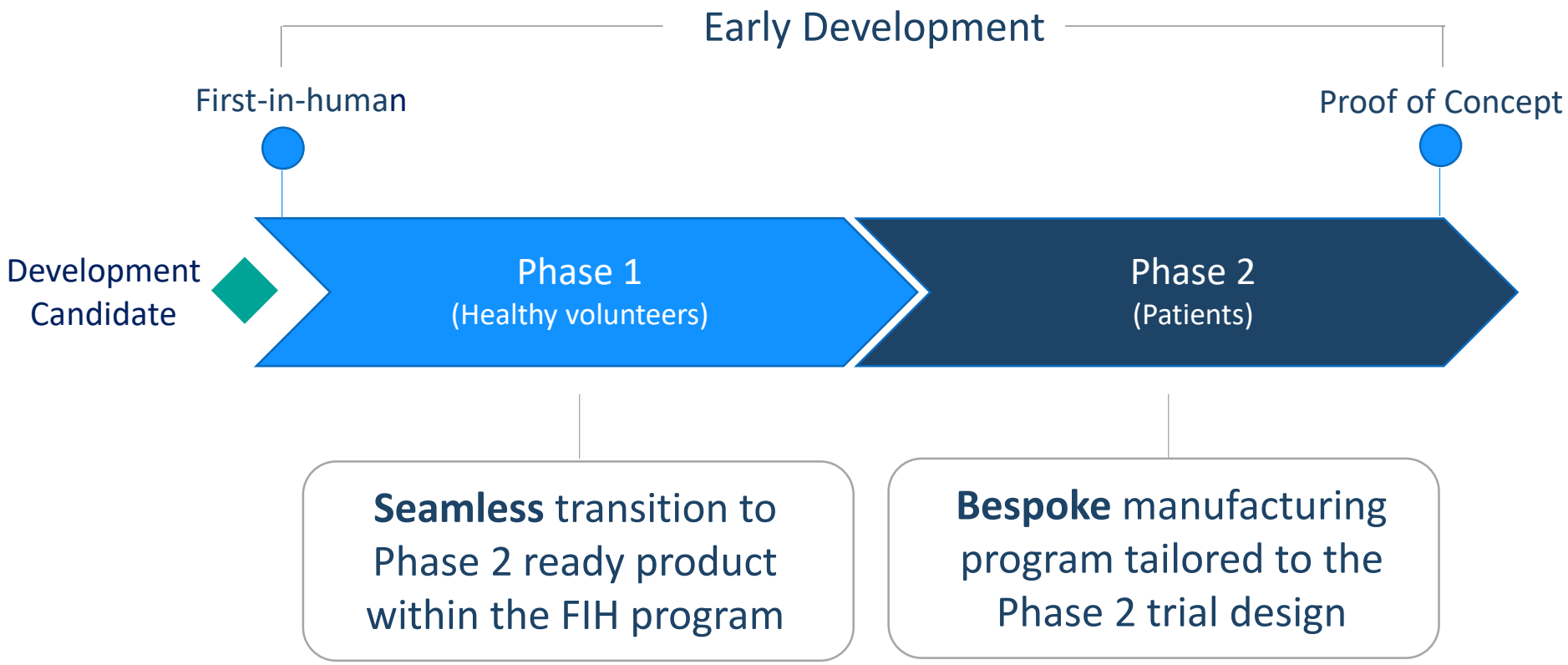
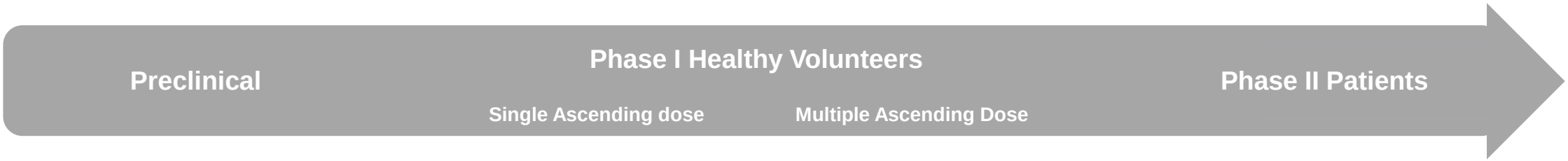
How can assessment to patient Proof-of-Concept (POC) be accelerated?

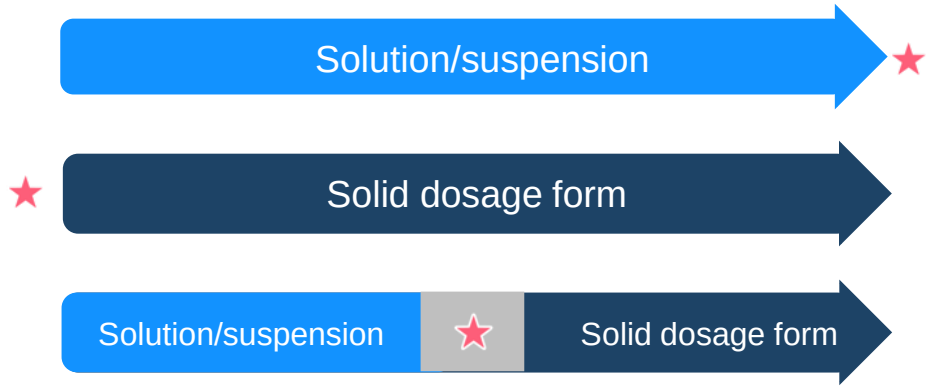


Integrated early development programs



Drug product strategies in early development: the status quo





- Phase I formulations are not likely to be suitable for patient trials
- A dosage form change will be required as the molecule progresses in development
- There are several potential drug product switching points ★

Translational Pharmaceutics: accelerates timelines and reduces costs

Innovation

Skills

Agility

Translational Pharmaceutics

Formulation

Manufacturing

Clinical

- Single integrated project team
- Accelerates development by > 12 months
- > 400 programs completed

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-020-00172-w

DIA

ORIGINAL RESEARCH

Check for updates

The Financial Benefits of Faster Development Times: Integrated Formulation Development, Real-Time Manufacturing, and Clinical Testing

Joseph A. DiMasi, PhD[1] · Michael Wilkinson, MPH[1]

Received: 10 March 2020 / Accepted: 28 May 2020

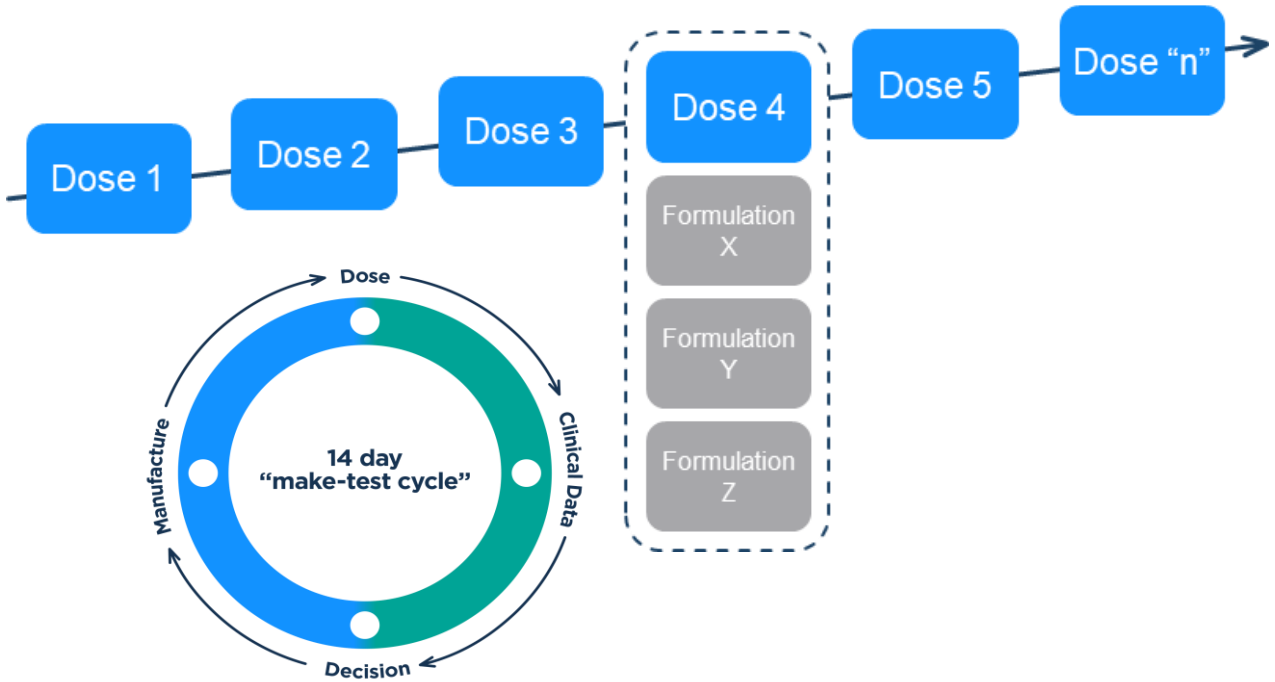
Abstract

Purpose Faster drug development times get new therapies to patients sooner and financially benefit drug developers by shortening the time between investment and returns and increasing the time on the market with intellectual property protection. The result is enhanced incentives to innovate. We provide a real-world example of the financial gains from quicker development using recent estimates of drug development costs, returns, and estimates of time reductions from an alternative early-stage drug development paradigm.

Identifying the Phase II POC drug product within the FIH program

Phase I in Healthy Volunteers

(Single & Multiple Ascending Dose)



Drug products prepared "real-time"

Features

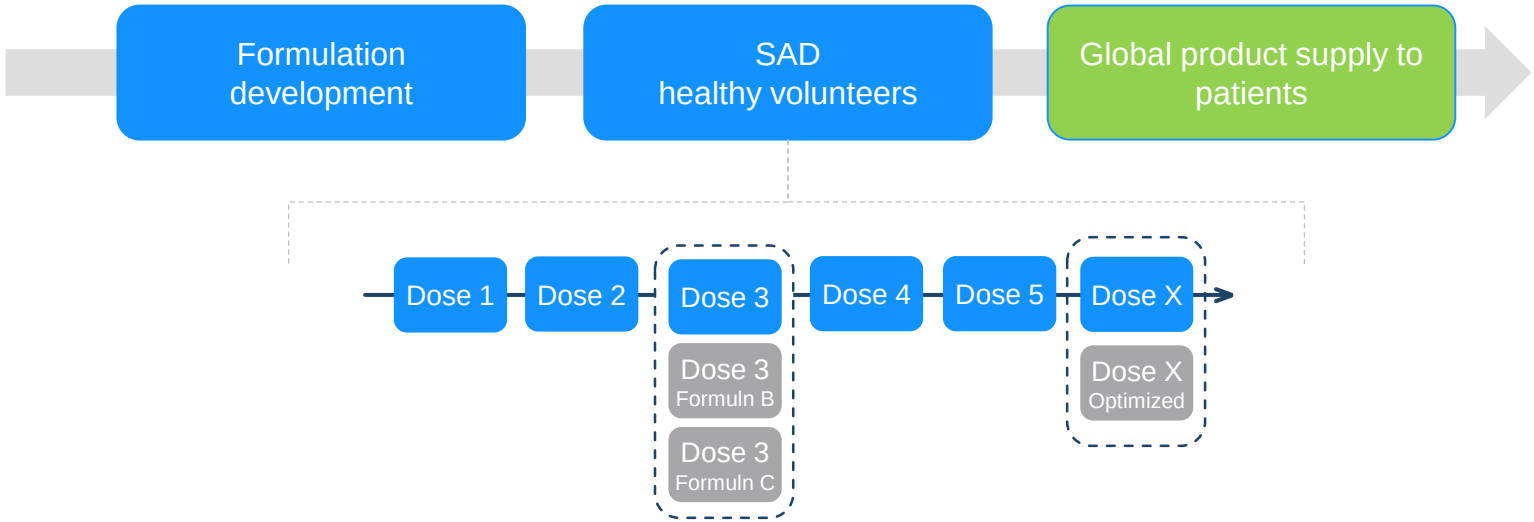
- Dosage form assessment within the FIH program
- Rapid make-test cycles of days rather than months
- Formulation selection based on clinical data
- Primary objectives of safety & tolerability maintained
- Minimization of CMC investments

Enables

- Precision in dose escalation
- Formulation screening and dosage form bridging
  - Simple to complex products
  - Solution to solid oral dosage form
  - Assessment of solubilization technologies
  - Immediate release to modified release

All achieved in a single clinical protocol

Case study: Formulation selection and seamless transition to patients



Background:

- US Biotech with poorly soluble molecule & goal of accelerating to patient trials

Program design:

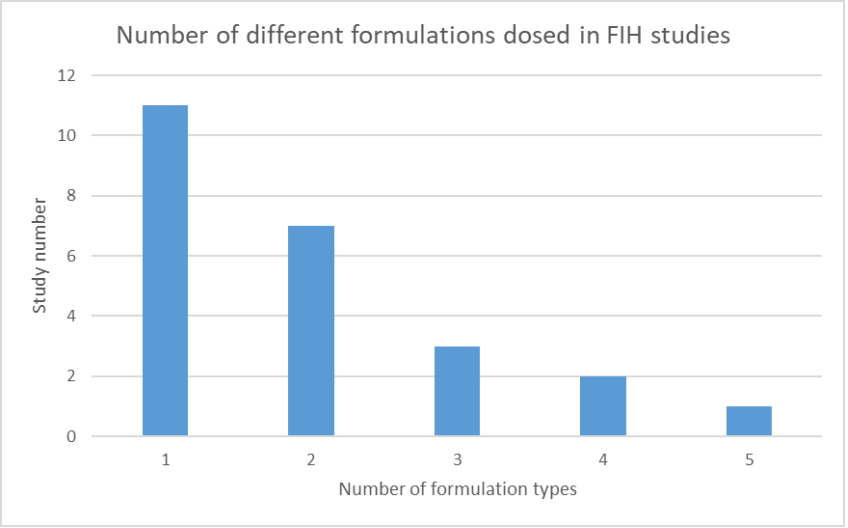
- Developed and evaluated 3 solubilization technologies during the FIH study

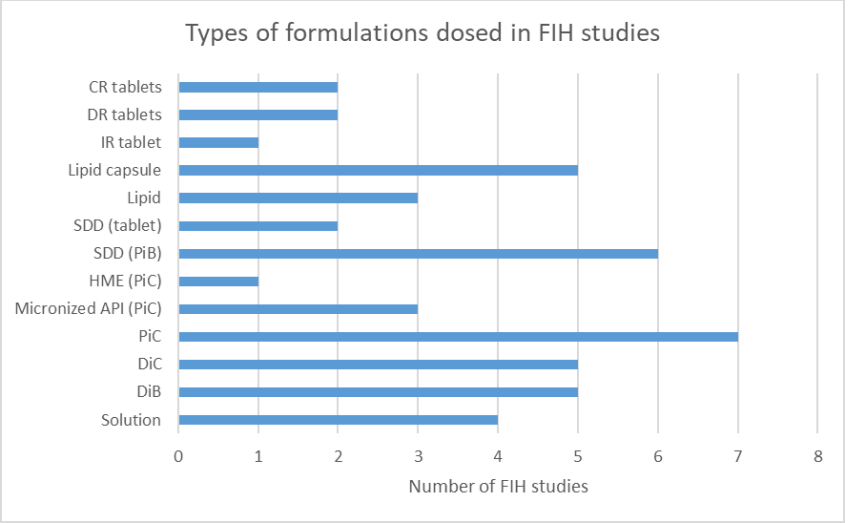
Outcomes:

- Identified drug product suitable for patients and optimized the powder blend
- Product supplied seamlessly into POC study within 12 months from start of formulation development

Formulation flexibility in FIH studies

- **Most recent FIH studies reviewed (n=24)**
- **>50% studies evaluated >1 formulation type**
  - Range from 2-5 technologies
- **Wide range of FIH formulations deployed**
  - 13 different product types
  - 4 “simple” first-for-purpose systems
  - 6 utilized bioavailability enhancement technologies
  - 3 evaluated tablets formulations
- **22 had flexibility on formulation composition**
  - Within-study adjustments in response to arising data
  - Dose, functional excipients





Benefits of formulation flexibility in FIH studies

- ✓ Start with “fit-for-purpose”, exit with “patient-ready”
- ✓ Formulation strategy driven by molecule properties
- ✓ Mitigation of biopharmaceutic risks
- ✓ Clinical data drive decisions
- ✓ Seamless transition of product to patients
- ✓ Controlled CMC investment profile
- ✓ Timeline optimisation to POC inflection

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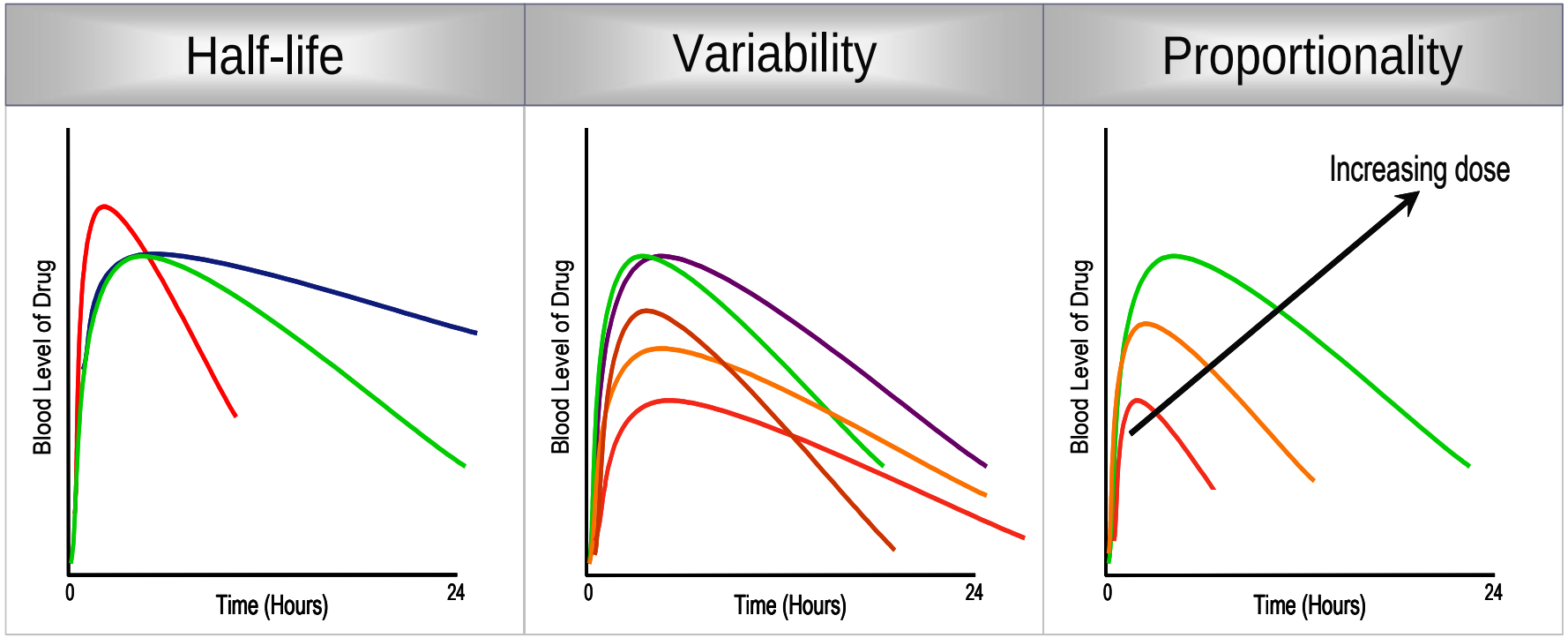
Post FIH/POC – addressing developability issues

Sub-optimal PK profiles

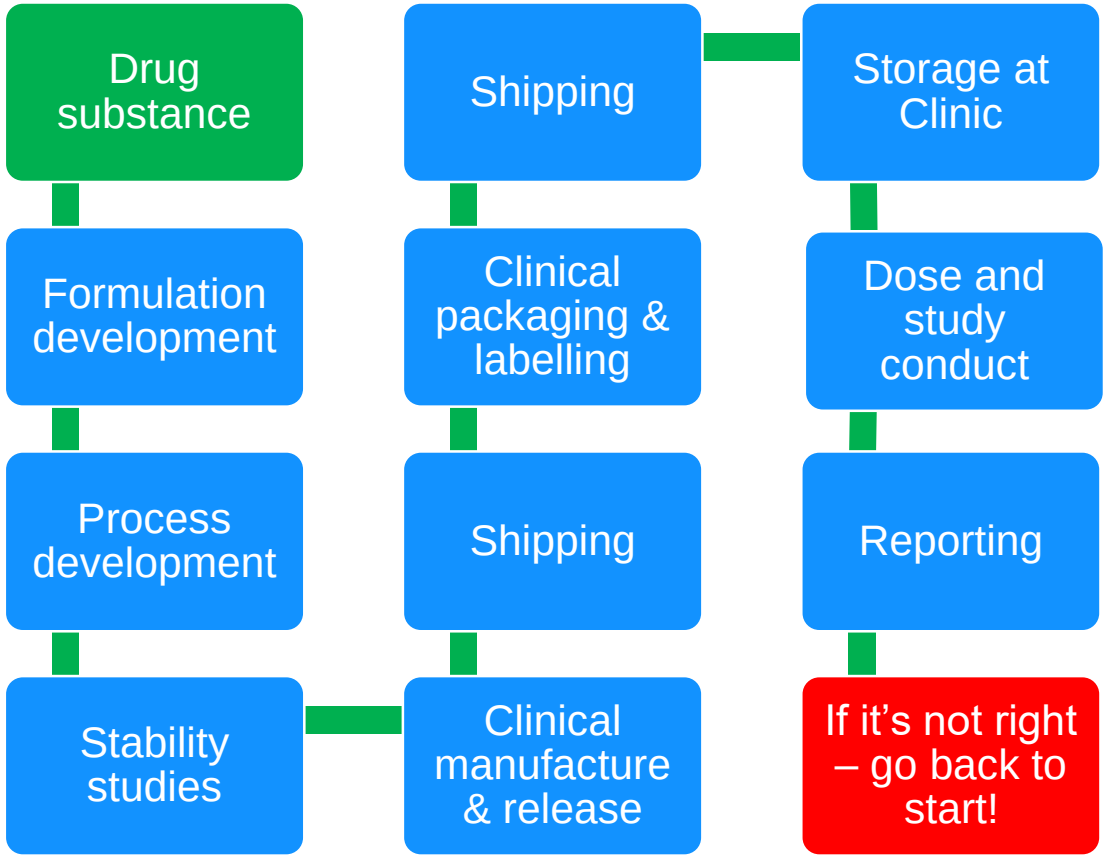


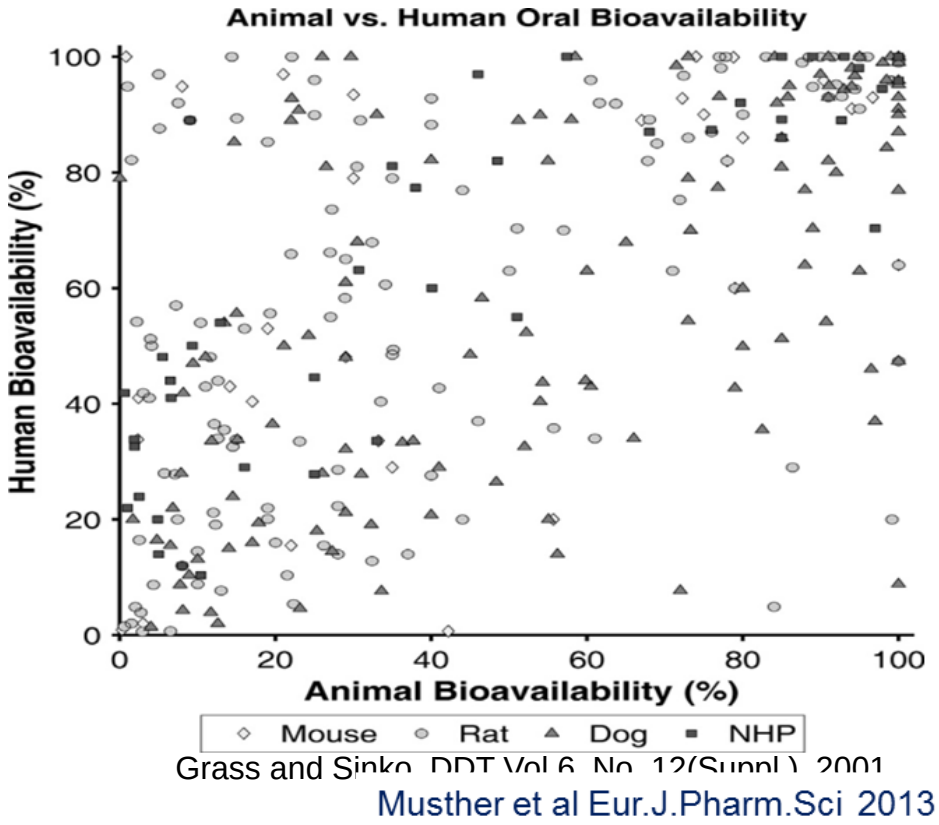
- **Not to mention……**
  - Poor exposure
  - Positive or negative food effects

Common shortcomings in PK profiles

Issue	Solution?
Cmax driven adverse events	Blunt Cmax via modified release formulation
Half-life too short for once daily dosing (<6h?)	Modified release formulation to provide sustained input function (caution over GI regional bioavailability)
High PK variability	Depends – is it input driven (formulation can help), if its elimination driven little opportunity (genotype screen?)
Poor exposure / non-linearity due to solubility limitation	Use of enabled formulations, if chemistry is locked
Extensive CYP mediated gut wall metabolism	Consider colonic delivery given lower CYP expression (caution over colon solubility/permeability)
Extensive CYP mediated first pass metabolism (gut wall & hepatic)	Consider non-oral route e.g. sublingual, rectal
Transporter efflux	Consider lipidic vehicles with potential to inhibit e.g. Pgp efflux (Vitamin E TPGS, Cremaphor, Labrasol)
Dose and/or time dependent changes to PK	Depends on saturable or induced processes
Performance affected by GI conditions (e.g. food, pH)	Food – develop formulation to replicate food effect when fasted pH – local pH modifiers / buffers within formulation

Non-integrated supply chains – a game of snakes and ladders?





Grass and Sinko DDT Vol 6 No 12(Suppl) 2001

Musther et al Eur.J.Pharm.Sci 2013

- X Significant time and cost
- X Many departments, organisations & locations
- X No flexibility when you get to the clinic
- X Formulations selected from in vitro & pre-clinical data

Integrated development

- Formulation technologies

1 2 3 4 5

- Formulation development
- Analytical methods
- Technical batches

Pharmaceutical development program

- Multiple prototypes
- Batch size <250
- 12-20 healthy volunteers

Clinical PK study

Period 1

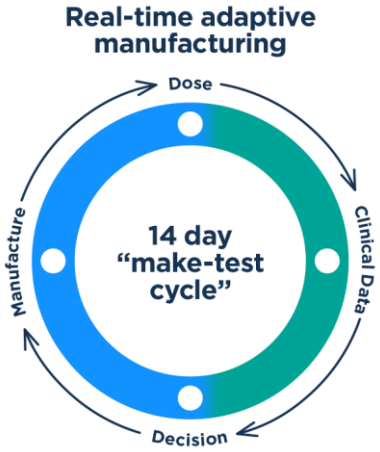
Period 2

Period 3

Period 4

Period 5

- ✓ Tablets
- ✓ Capsules
- ✓ Multiparticulates
- ✓ Granulation
- ✓ Spray drying
- ✓ Coating
- ✓ Particle size reduction
- ✓ Lipids
- ✓ Parenterals
- ✓ Non-oral delivery



Case study: Solubilization technology selection post FIH

Pharmaceutical development program

Three formulation technologies
1. Micronized blend in capsule
2. Self-emulsifying lipid based capsule
3. Spray-dried dispersion (SDD) tablet

Clinical PK study

- Period 1: SDD Tablet
- Period 2: Micronized capsule
- Period 3: Lipid based capsule
- Period 4: Drug-in-Capsule reference
- Period 5: Selected Formulation Fasted
- Period 6: Selected Formulation Fed

Real-time adaptive manufacturing

Interim decision

Background: BCS class II molecule with poor oral bioavailability & large food effect

- Quotient designed the formulation strategy & completed a 12 week program
- Sequential clinical study in 16 healthy volunteers
- Human data selected the simpler and cost effective micronized formulation
- Program delivered data to support future product development strategies
- Timeline: Laboratory start to clinical PK data in 6 months

W1030-04-23

A Phase I Study Allowing Clinical Screening of Multiple Solubility-Enhancement Formulation Technologies, and an Assessment of Food, PPI and Dose Linearity Assessment with the Selected Formulation of BOS172767, in Healthy Volunteers

Vanessa Zann[1] , Litza McKenzie[1], Kieran Crowley[1], Sue Sweet-Smith[1], Anjumn Shabir-Ahmed[1], Karen Andreas[2], Richard Mountfield[2], Ashley Milton[3]

1. Quotient Sciences, Nottingham, UK 2.Boston Pharmaceuticals Inc., Cambridge, MA, USA 3.GSK, Waltham, MA, USA

CONTACT INFORMATION: +44 (0)115 974 9000 (UK) +1-800-769-3518 (USA) info@quotientsciences.com

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PURPOSE

BOS172767 is a first in class small molecule inverse agonist of retinoic acid-related orphan nuclear receptor gamma-t, being developed for the treatment of autoimmune diseases. Safety and tolerability have been demonstrated in a previous first in human (FIH) Phase 1 study using a simple API blend in capsule.

Low oral exposure, non-linear pharmacokinetics (PK), high variability and a large positive food effect were observed. Therefore, a solubility enhanced formulation was considered necessary to help overcome these PK challenges and identify a formulation suitable for long-term clinical development.

Formulations were developed and screened using an integrated platform of real-time adaptive GMP manufacturing and clinical testing. The study was designed to assess the clinical performance of three prototype formulations, assess food effect and dose linearity of a selected formulation and also the impact on exposure in subjects taking proton pump inhibitors (PPI). The clinical PK data generated in the study would then be utilized to select a formulation for further development.

METHOD(S)

Three different formulations, representing different strategies (micronized capsule, lipid capsule, and spray dried dispersion [SDD] tablet) were developed and assessed in a pH shift biorelevant dissolution test using fasted state simulated gastric and simulated intestinal fluid. The aim of the biorelevant dissolution test was not to rank order the formulation platforms but rather identify optimal dissolution profiles for each platform.

An integrated Translational Pharmaceutics program was designed to evaluate the human PK of the multiple formulations manufactured to GMP at small-scale. An adaptive design allowed a within-trial decision (see schematic) to select the optimal formulation for additional clinical testing in the same study protocol.[1]

The study was open label, with two parts in healthy subjects. Part 1 was a 6-period sequential, part randomized study, in which 12 subjects received three formulation prototypes and the IR reference capsule at 200 mg in the first four periods. After period 4 the lead formulation prototype was then selected for dosing in the fasted and fed state.

The lead formulation advanced to optional Part 2, a 4-period sequential study in 10 healthy subjects, assessing exposure at 3 single ascending dose levels and in subjects taking PPI.

RESULT(S)

In vitro dissolution testing demonstrated that all three formulation technologies had greater % release (50 to 63 %) compared to the FIH API blend in capsule and IR reference capsule, which had < 20 and < 10 % at 90 minutes, respectively.

In Part 1, all prototype formulations at 200 mg (SDD tablets, lipid capsules and micronized capsules) showed an increase in exposure (Cmax and AUC(0-last)) over the IR reference capsule (Figure 1), with all prototype formulations showing similar AUC(0-last). The SDD tablet had the highest exposure showing an approximate 10-fold increase in Cmax and a 2-fold increase in AUC(0-last) compared to the reference capsule. The micronized capsule was selected for progression due to future manufacturing considerations, similar exposure to that of the SDD tablet, and a lower observed Cmax which could potentially provide an improved safety profile.

The micronized capsule was then dosed at 100 mg in the fed (high fat meal) and fasted state during periods 5 and 6. Cmax increased by > 2-fold, however the AUC(0-last) was similar to that in the fasted state. The magnitude of the food effect was reduced compared to that observed in the previous study with the FIH API blend in capsule, whereby a 5.6 and 3.2-fold increase in Cmax and AUC(0-t) was observed with a 200 mg dose, respectively. A level C in vitro in vivo correlation (IVIVC) was achieved for % dissolution at 90 minutes and AUC(0-last) (Figure 2), thus the biorelevant dissolution test has been shown to be clinically relevant.[2]

In Part 2, with dose escalation of the micronized capsule at 400 mg, 600 mg and 800 mg exposure increased in an approximate dose proportional manner, although data was highly variable (Table 1). Previously, with the API blend in capsule systemic exposure had plateaued at 200 mg. Co-administration with the PPI rabeprazole resulted in minimal effect on exposure (Table 1). Overall the incidence of adverse events for Part 1 and 2 was low, with no SAEs.

Figure 1: Mean Plasma BOS172767 Concentration-Time Profiles after Oral Dosing on Semi-Log Scale (Part 1)

Figure 2: Level C IVIVC – Correlation between % dissolution at 90 minutes and AUC(0-last) for solubility-enhanced formulation prototypes and API reference capsules

Table 1. Summary of the Geometric mean (%CV) Key Pharmacokinetic Parameters of BOS172767 in healthy volunteers following oral administration of Micronized Capsule – Part 2

	Tmax (h)*	Cmax (ng/mL)	AUC (0-48h) h*ng/mL	AUC(0-inf) (h*ng/mL)
400 mg (N=10)	3 (1, 24)	41.5 (66.7)	828 (67.1)	- (n=2)
600 mg (N=10)	2.51 (1, 36)	56.5 (93.5)	1320 (80.2)	-
800 mg (N=9)	3 (1, 6)	78.9 (121)	1600 (82.6)	2650 (88.2) (N=6)
600 mg + PPI (N=9)	4.51 (2, 24)	47.4 (66.8)	1160 (73.2)	2350 (38.4) (N=6)

*Median (range), mg = milligram, H = hour, ng = nanogram, mL = millilitre, N = number, CV = coefficient of variation

IR – IR reference capsule, FIH – API blend in capsule (dosed previously in the FIH study), Micro – micronized capsule, Lipid – lipid capsule, SDD – SDD tablet

CONCLUSION(S)

Translational Pharmaceutics was used to evaluate three BOS172767 formulations in one integrated clinical study, and successfully identified the micronized capsule as the new lead formulation. This formulation had superior exposure compared to the IR reference capsules, and approximate proportional increase in exposure up to 800 mg. The food effect observed at 100 mg was reduced compared to that previously seen at 200 mg (FIH capsule) and elevated gastric pH (subjects taking PPIs) had minimal effect on exposure. A Level C IVIVC was achieved with a biorelevant dissolution test, which provides valuable information for future formulation development and setting of product specifications.

REFERENCES

1. McDermott J, Scholes P. Formulation design space: a proven approach to maximize flexibility and outcomes within early clinical development. Therapeutic Delivery. 2016;8(11):1269-1278.

2. Suarez-Sharp S, et al. Regulatory Experience with IVIVC in NDAs. The AAPS Journal. 2018. Nov (18) 1379-1390

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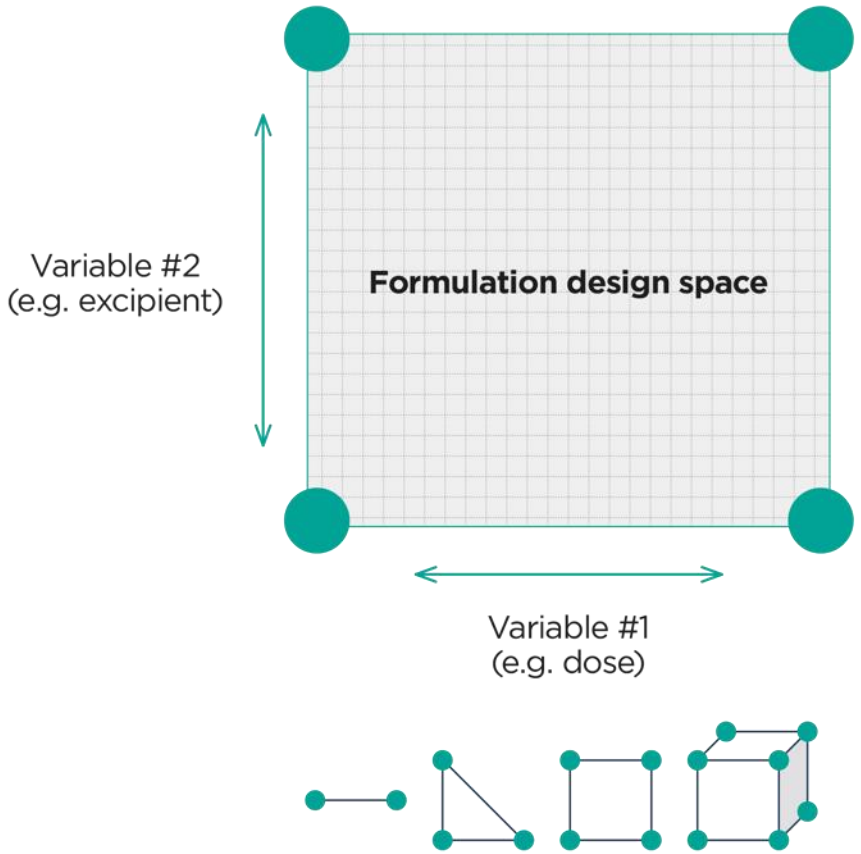
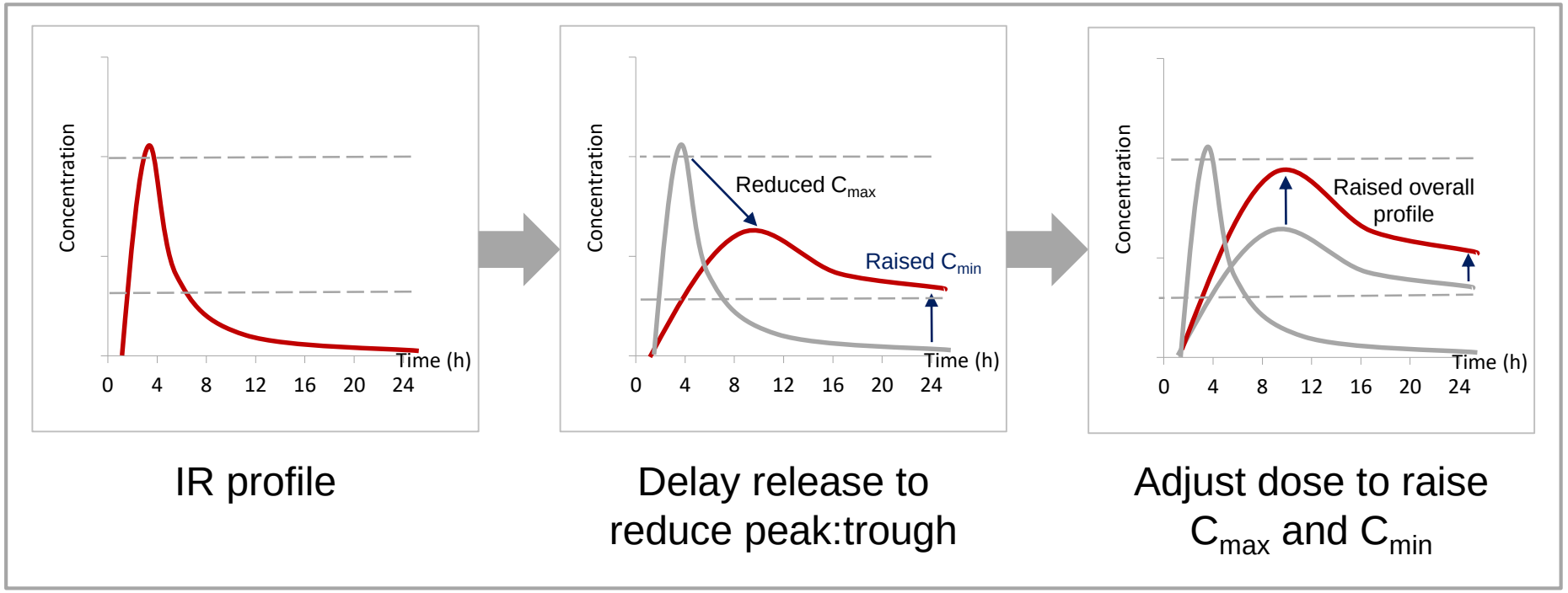
Formulation design spaces are used to enhance flexibility



- Demonstration data generated on corner points, compositions bracketing the entire design space
- Any formulation within the design space may be manufactured and dosed
- No regulatory amendments or notifications
- Compositions selected based on emerging clinical data
- Investigate multiple formulation parameters
  - Drug dose/concentration
  - Functional excipient content
  - Drug:polymer ratio
  - Surface area volume ratio
  - Coat composition/thickness

Utilizing design space to optimize clinical PK

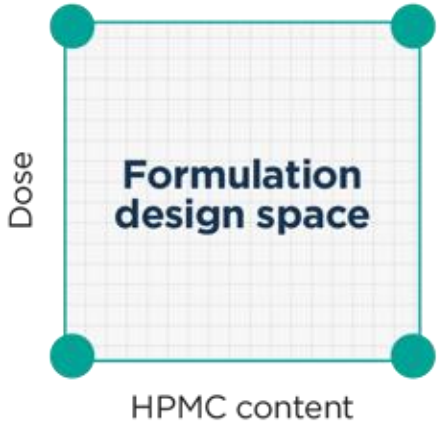
- **Numerous technologies are available to modify drug release, the difficulty is identifying the right composition to hit a target in humans**
- **Quotients design space approach allows within-trial flexibility to adjust the formulation based on emerging PK (and safety) data**



Case study: Modified release development

Pharmaceutical development program

- Matrix tablet formulation development
- Technical batches
- 14 day stability data

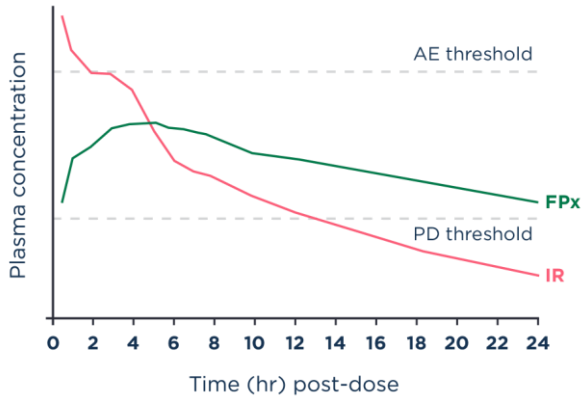


Clinical PK study

- Period 1: Reference
- Period 2: Prototype 1
- Period 3: Prototype 2
- Period 4: Prototype 3
- Period 5: Food effect

Real-time adaptive manufacturing

Study outcome



Background: Cmax related AE's, BID dosing with IR formulation

- Quotient selected to develop once-daily MR formulation
- Sequential clinical study in 15 healthy volunteers
- Formulation optimized in response to clinical data
- Product defined in 3 test periods and lack of food effect established
- Timeline: Formulation development to clinical report in 7 months

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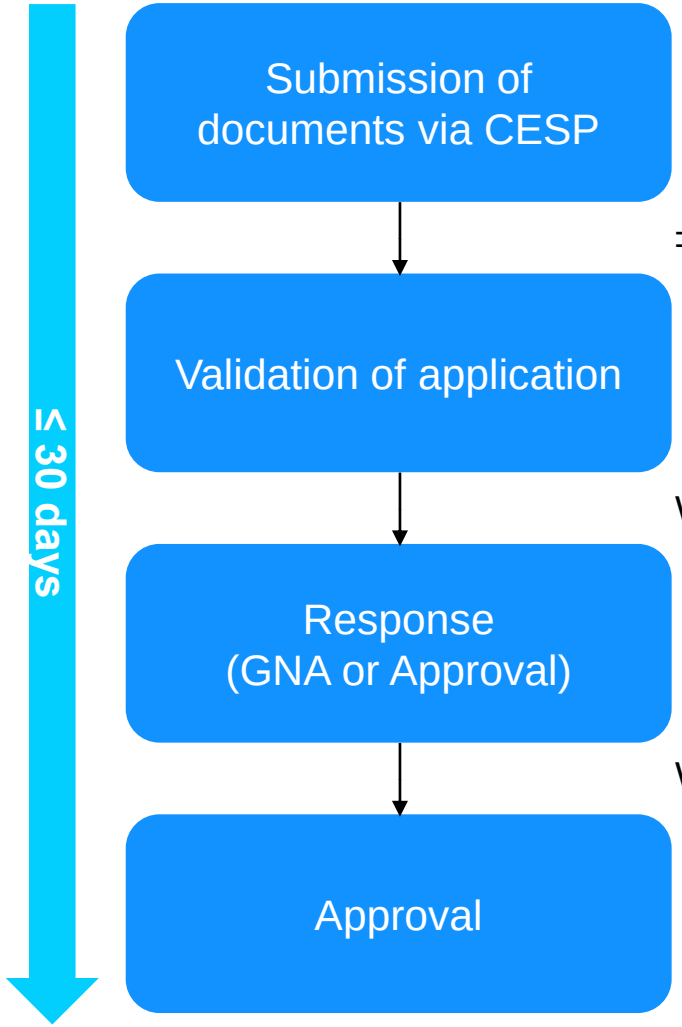
Regulatory framework

MHRA: Rapid approval process for Phase 1 submissions



- *Clinical Protocol*
- *Investigator Brochure (IB),*
- *IMPD (drug substance, drug product(s), risk/benefit assessment)*

±2 days

Within 14 days

Average time for initial review of Phase I submissions was 12.29 days in 2019
MHRA Annual report 2019-20

Within 14 days

CESP = Common European Submission Portal (to be superseded by MHRA portal in Jan'21)

GNA = grounds for non-acceptance

MHRA: EAG and Inspectorate

- **Expert Advisory Group – Clinical Trials, Biologicals and Vaccines**
  - Set up post TeGenero incident
  - Additional review for some submissions (most cases not needed)
    - FIH with new compounds acting (directly or indirectly) via immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action not well characterised.
    - FIH with novel compounds acting via possible/likely species specific mechanism
    - Any FIH studies which are otherwise seen as requiring expert advice

- **Inspections**
  - Regular GCP & GMP facility inspections every 2-3 years
  - In addition (voluntary) Phase 1 accreditation scheme (clinic units)
    - Focus on suitability for FIH studies & high-risk molecules (EAG review)
    - http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con2033097.pdf

Ethics - REC (Research Ethics Committees)

- **Submissions**
  - Ethics governed in England via HRA (Health Research Authority [est. 2011])
    - Statutory, non-departmental public body
  - Approximately 20 RECs in UK can review Phase I trials
  - Applications includes:
    - Clinical protocol, Investigator's Brouchure (IB), Informed Consent / Patient Information (ICF), insurance details
  - Statutory timelines – 60d approval
    - 2019 average approval time 31 days (Quotient data)
  - HRA approval also required if research is within the NHS

- **No inspections**
  - SSI (site specific information) submissions also go to the main REC to approve the site.
  - The REC may want to visit the site periodically unless the clinical unit has MHRA accreditation (standard or supplementary) – which is normally the case
    - Granted by MHRA GCP Inspectorate via the inspection (every 2-3 years)

Good Clinical Practice – grey guide 2012

- **“Legislation, guidance and good practice that relates to the conduct of clinical trials of medicinal products for human use in the UK”**
- **Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH E6)**
- **Provides public assurance that trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (1964)**
- **It is a set of guidelines which must be followed when conducting clinical trials to ensure that;**
  - The rights and well-being of clinical trial subjects are protected
  - The resulting data are valid

Grey guide contents….

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Summary

Summary

- **Recent Incidents have influenced FIH study designs – now safer**
  - Dose selection criteria increasingly defined by pharmacology rather than toxicology
  - Minimising risk to subject safety is the most important aspect of a FIH study
- **Understanding developability potential, risks and challenges is also a key focus**
  - Inclusion of biomarkers and PD assessments in FIH studies
  - Understand formulation and drug delivery requirements early
- **Speed to a well-defined POC is key**
  - Interleaved SAD/MAD, multi-part protocols, rapid transition into patients
- **Scientific and operational integration is critical to improving R&D productivity**
  - Use of human data to drive decisions
  - Formulation flexibility to address biopharmaceutics challenges
  - Seamless transition from volunteers to patients
- **UK regulatory framework is supportive of speed, flexibility and innovation**

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Any questions?

peter.scholes@quotientscences.com

Regulatory Clinical Pharmacology studies

- **Food interaction study**
  - Does a high fat meal effect the PK?
- **QTc study**
  - Does the IMP have an effect on the QT-interval of the ECG
- **Special populations**
  - Hepatic or renal impairment groups
- **Gender / Age / Genetic differences study**
  - Are there any population factors which effect the PK or tolerability of the new drug?
  - e.g. CYP2D6, CYP2C9 and CYP2C19
- **Human ADME study**
  - Mass balance, routes rates of elimination
  - Metabolite profiling and identification
- **Drug-drug interaction studies**

Studies will depend on drug properties, intended therapeutic target and preclinical data