Integrating adaptive pharmaceutical and clinical strategies to improve flexibility and efficiency in early development.

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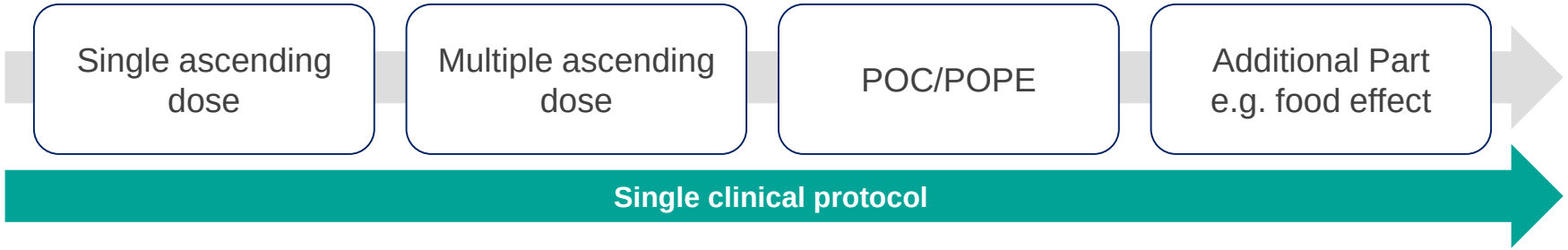
CSO, Quotient Sciences

AHPPI Annual Meeting 22nd June 2018

What do we mean by “integrating”?

- Dictionary definition:
  - “To put together parts or elements and combine them into a whole”

- Early phase studies have historically been performed as separate, stand-alone protocols
- 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



- **Are we maximising our potential in early development?**

What do we mean by “adaptive”

- Dictionary definition:
  - “Having an ability to change to suit different conditions”

- Adaptive clinical trials
  - “A study that includes a prospectively planned opportunity for modification of one or more specified **aspects of the study design and hypotheses** based on analysis of data (usually interim data) from subjects in the study *(FDA guidance)*
  - “A clinical trial that evaluates a medical device or treatment by **observing participant outcomes** (and possibly other measures, such as side-effects) on a prescribed schedule, **and modifying parameters of the trial protocol** in accord with those observations” *(Wikipedia)*
  - “An adaptive design is defined as a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. **The purpose is to make clinical trials more flexible, efficient and fast**” *(Chow et al 2005)*

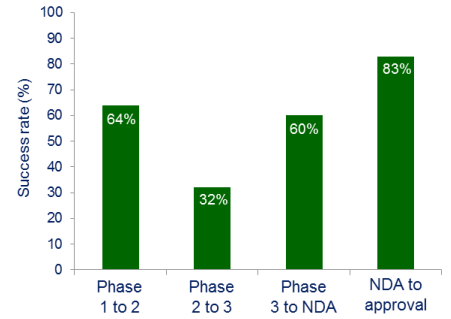
- **Are we maximising our potential in early development?**

Overview

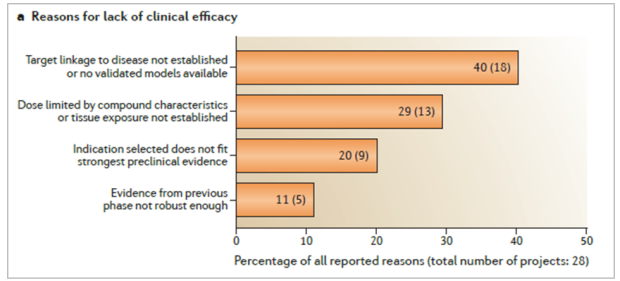
- Drivers for alternative approaches in early development – don’t forget the drug product
- Introduce Translational Pharmaceutics
  - Benefits of integrating GMP manufacturing and clinical testing
- Applications and case studies
  - Accelerating FIH to POC
  - Reengineering product optimisation
  - Personalised manufacturing for patient studies
- Summary

Key challenges in todays early development

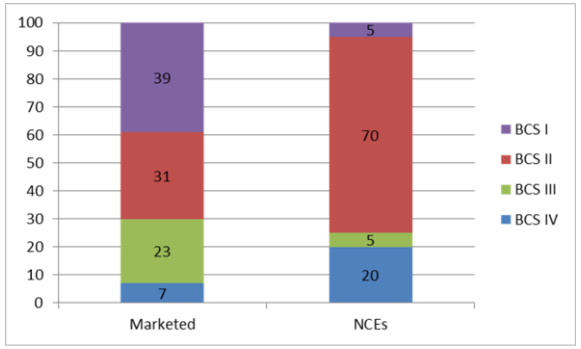
- Attrition remains high through the development life-cycle
  - 80% drug candidates have failed by end of Phase II
- Oral bioavailability and tissue exposure is still a key contributor
  - Cited as a reason for failure in ~30% of cases
- Physicochemical and biopharmaceutic properties are challenging
  - ~90% NCEs have poor solubility and/or permeability
- Integrated and adaptive clinical protocols alone will not address these development risks



Hay et al 2014 Nature Biotechnology 32(1) 40-51

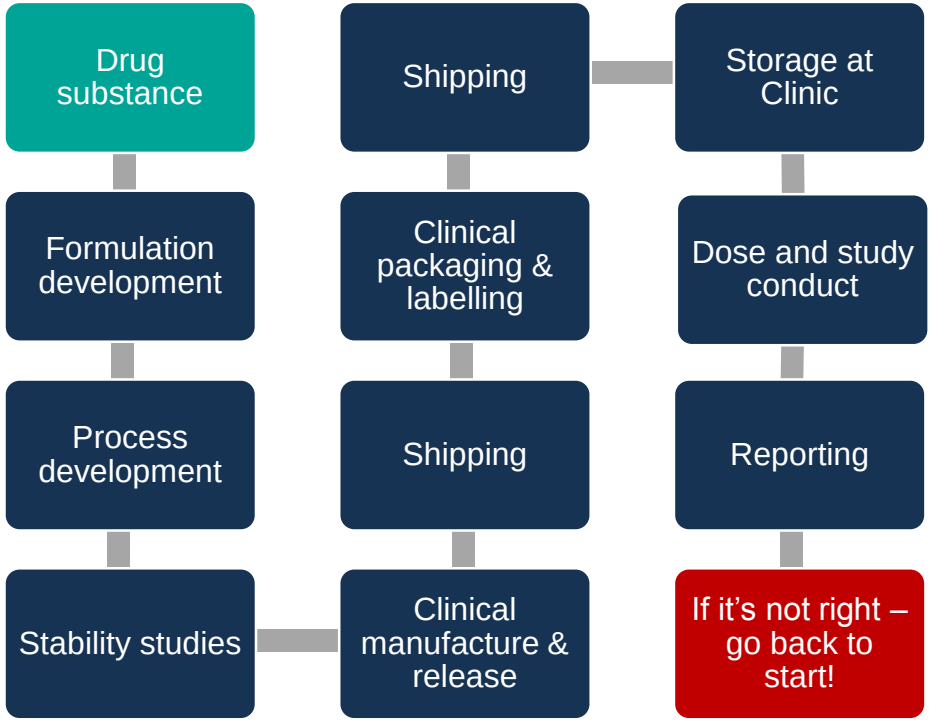


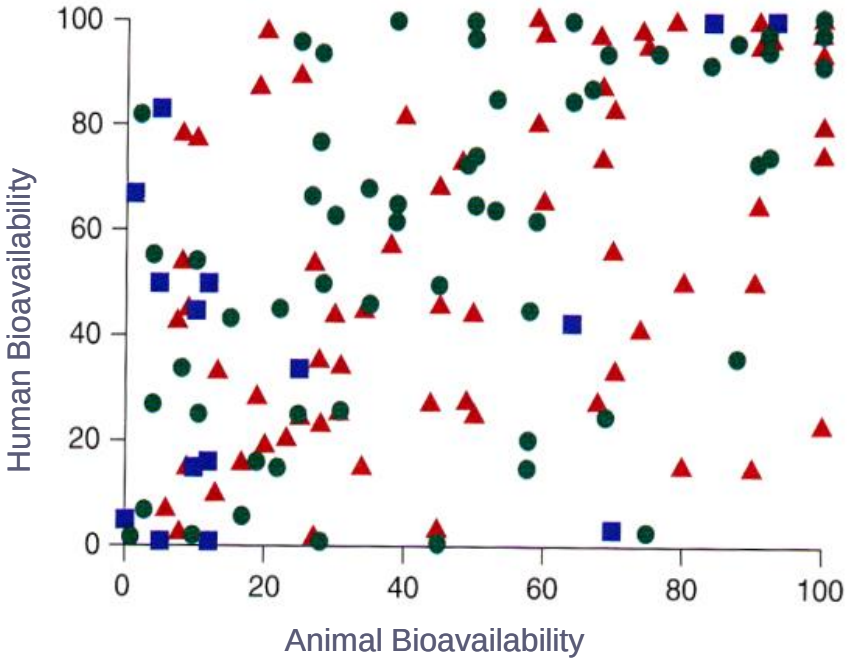
Cook et al 2014 Nature Reviews Drug Discovery 13 419-431



Quotient data

Getting the product to the patient





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

- Significant time and cost
- Formulations based on animal data
- Clinical testing restricted to pre-defined, pre-manufactured prototypes

Translational Pharmaceutics

Formulation development
Pharmaceutical analysis
Real-time adaptive GMP manufacturing

Make

API synthesis

Pharmaceutical development

Clinical trial supplies

Commercial manufacture

14 day cycle

Translational Pharmaceutics

Horizontal integration

Test

Laboratories

Healthy volunteers

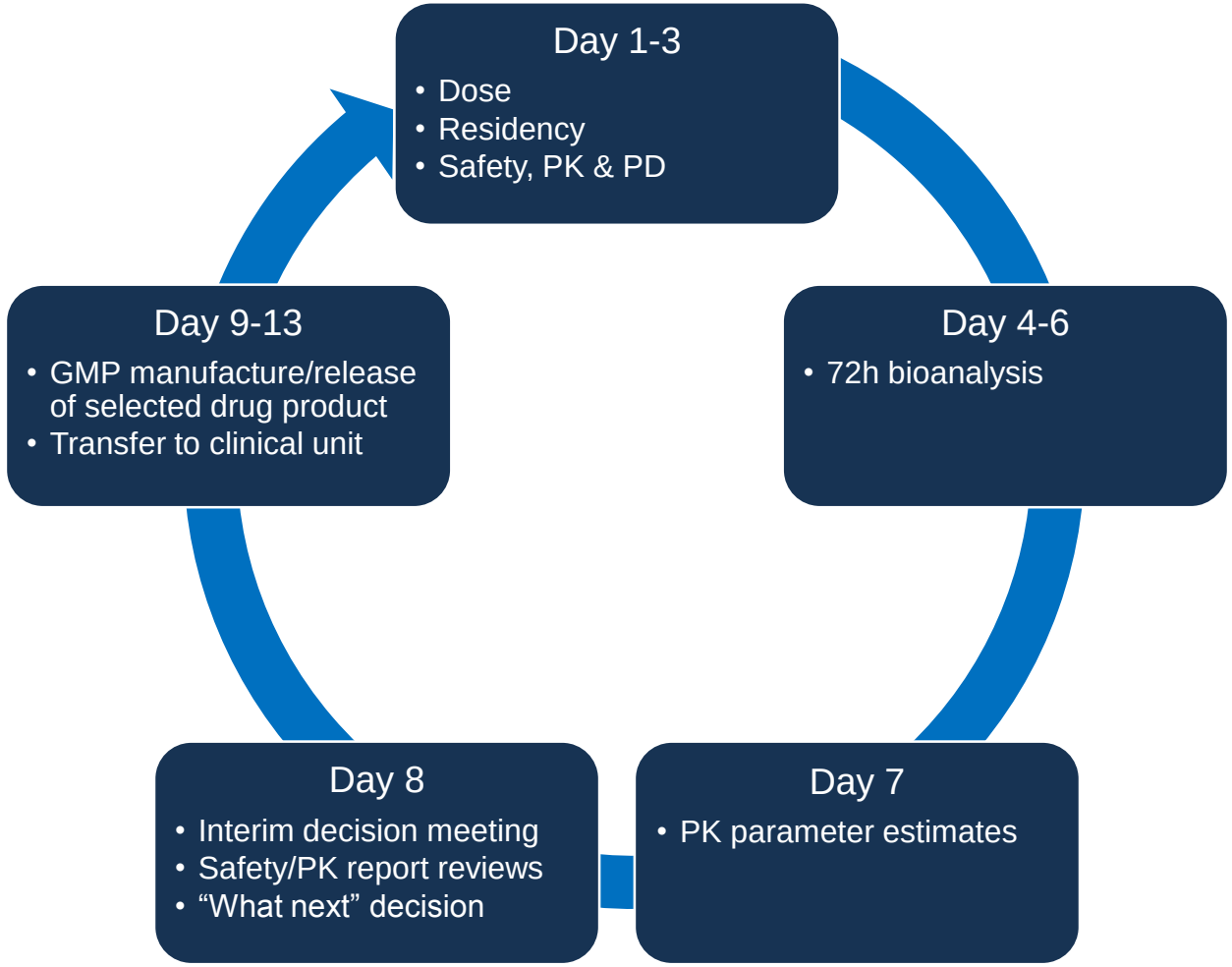
Patients

Commercial development

Clinical Pharmacology Unit
Regulatory affairs
Data analysis & reporting

The integration of formulation development, real-time adaptive GMP manufacturing and clinical testing

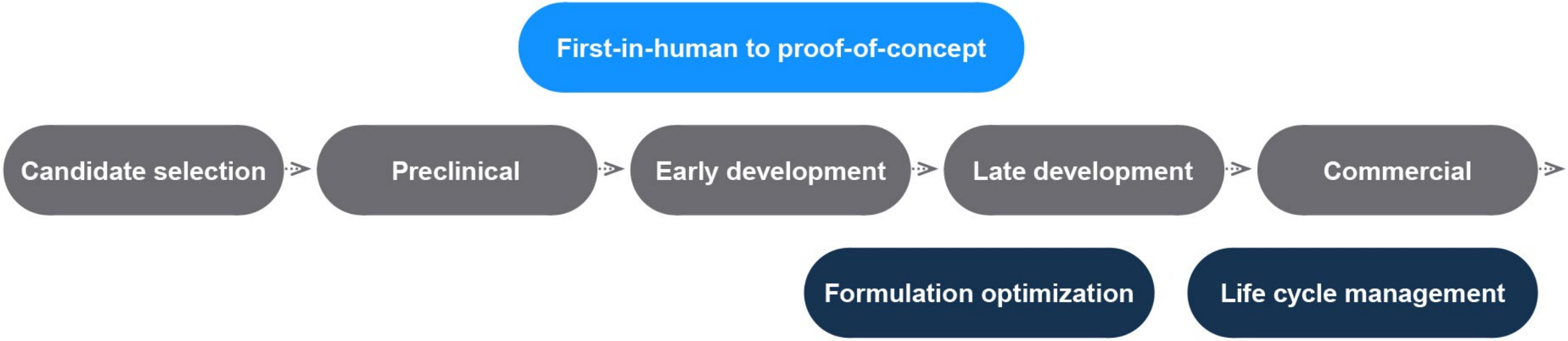
Transforming development into “make-test” cycles



Benefits to industry, regulators and patients

	Conventional GMP practice	Translational Pharmaceutics	Impact
Timeline savings	None	Typically ≥ 6 months	Accelerated POC, expedited formulation optimisation
CMC investment savings	None	Typically ≥ $500,000	Managed early R&D expenditure
API conservation	None	Up to 85% reduction	Improved efficiency
Flexibility	None (fixed compositions)	Adaptive within protocol	Enhanced decision making
Formulation selection	Based on surrogate tools	Based on clinical data	Increased precision and potential for success
Risk reduction of repeat	None	Enhanced	Reduced exposure of healthy volunteers to NCEs
Knowledge space build	Limited	High	Early application of ICH Q8 QbD principles

Translational Pharmaceutics - key applications



RapidFACT®
(Rapid Formulation development And Clinical Testing)

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Maximising the adaptive nature of Phase I studies

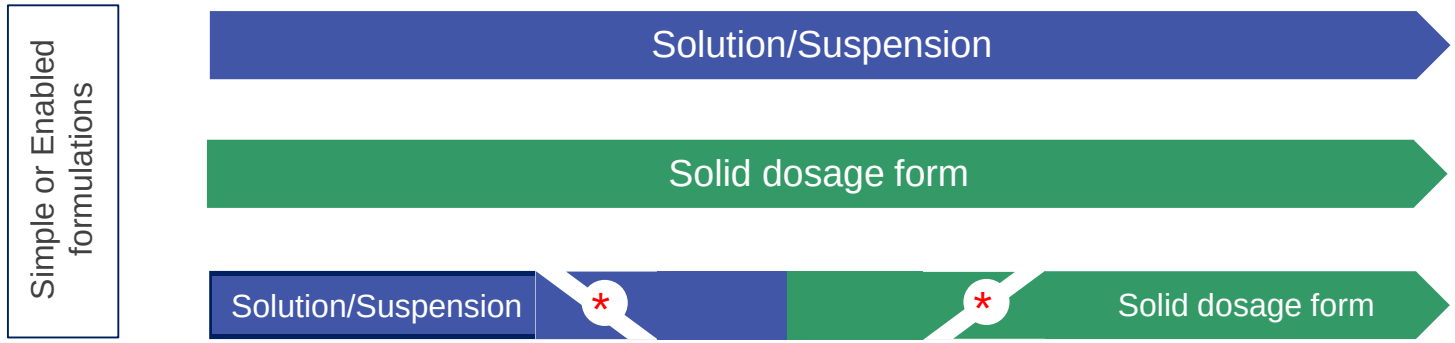
Accelerating FIH to POC

Early development strategy questions

Question: Is this typically 1 study? Or 2? Or 3?

✓

Question: How do you develop a suitable drug product for FIH and POC?



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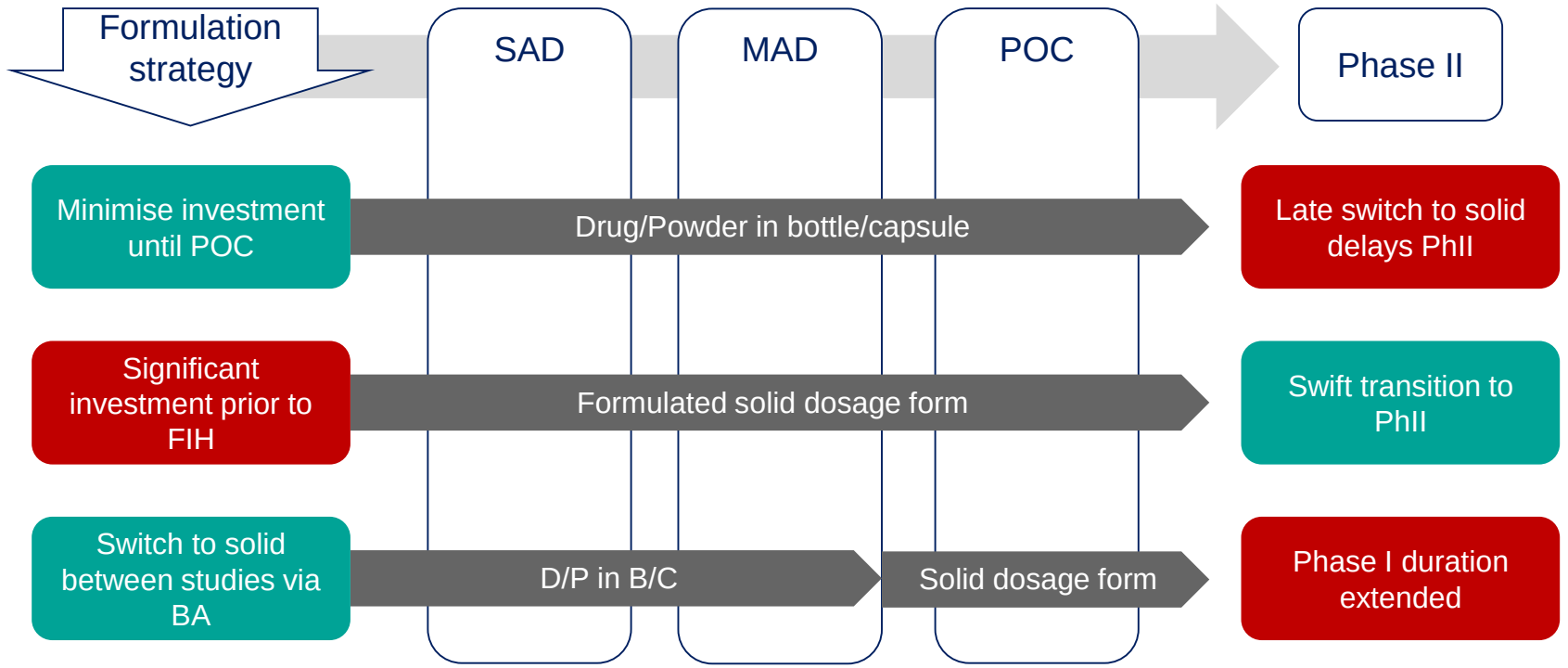
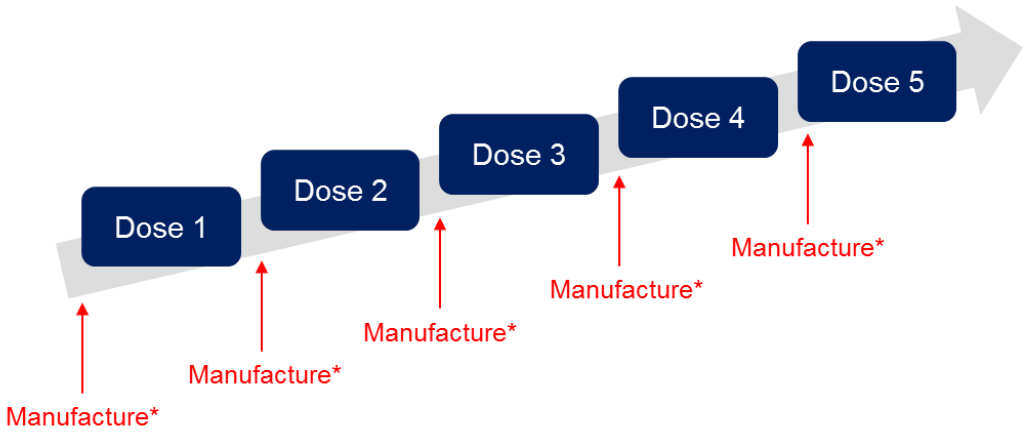
* Potential drug product switching points

Researchers encounter stark decisions



- How can we transition from a FIH formulation to a solid oral dosage form without delaying the pivotal patient studies?
- For every project it is a balance of science, time and cost

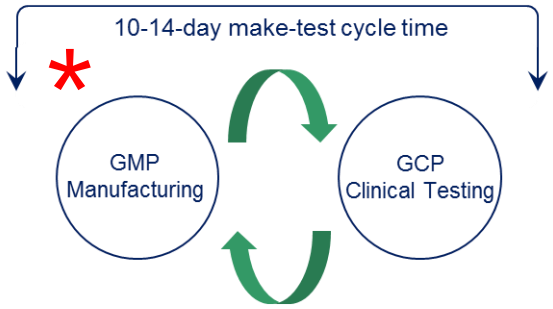
Real-time manufacture within a FIH program



- FIH design and objectives unaffected – assessment of safety, tolerability, PK, PD
- Emerging data reviewed by a SAC to determine dose progression
- 10 to 14 day interval between cohorts

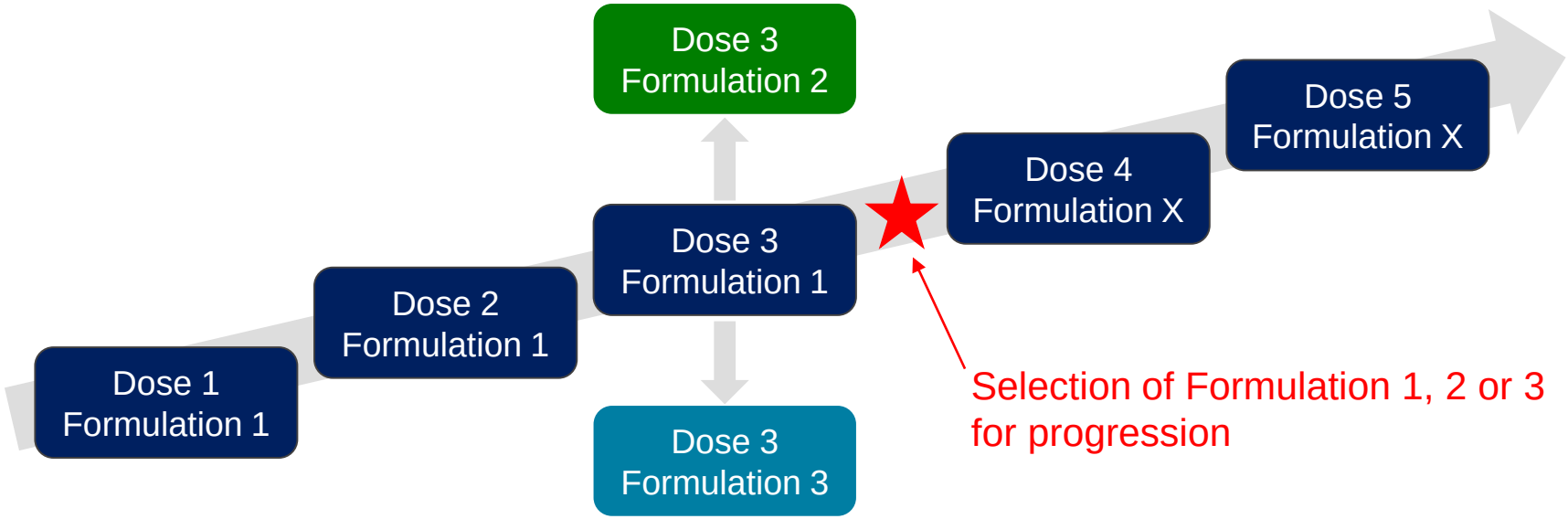
Additional benefits:

- Manufacture of product as needed, based on emerging clinical data
  - No need for bulk manufacture of pre-determined, fixed unit doses
- Conservation of API
  - Small batch sizes and only short term stability required
- Precise, fully flexible doses
  - Unit dose selected and manufactured based on emerging clinical data

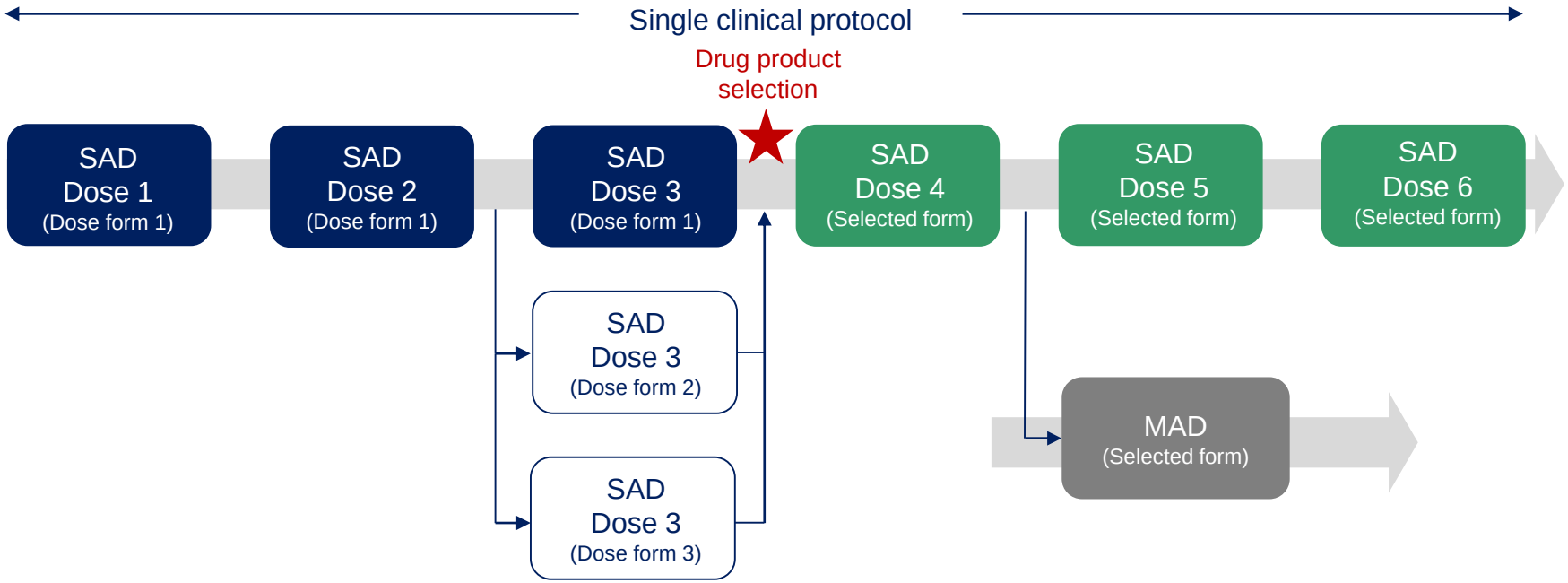


Drug product selection within a FIH program

- Why include flexible CMC strategies for FIH programs?
  - Following rapid FIH entry, switch to a solid oral dosage for POC/Phase II
  - Screen formulation technologies e.g. to overcome solubility challenges

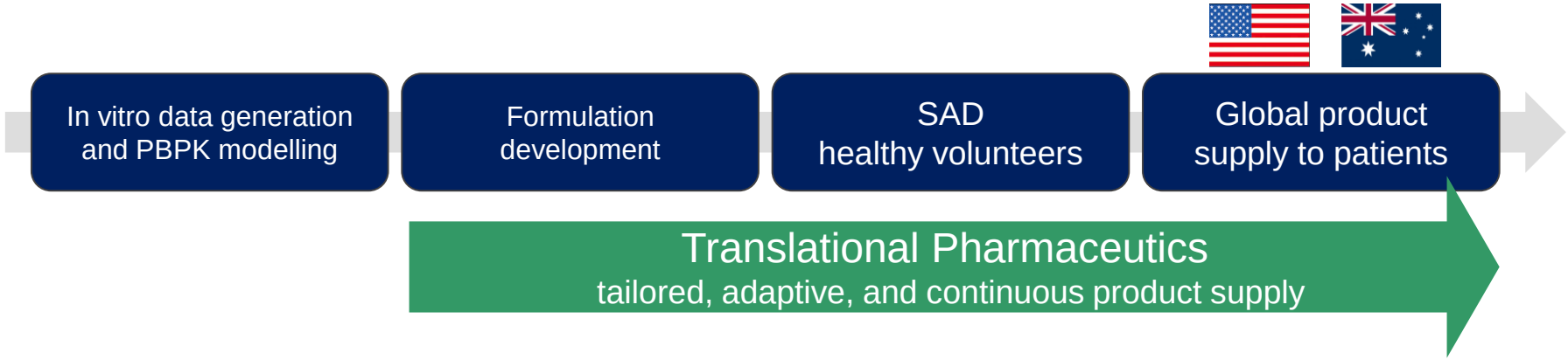


Case study:
Managing risk from preclinical PK



- Differences in bioavailability between solution vrs solid in preclinical species
- Within-study flexibility to test up to 3 formulations
- Single protocol and regulatory submission
- Standard MHRA approval time <20days
- Overall timeline <10mths
- Drug product selected for Phase 2

Case study:
FIH formulation assessment & seamless transition to patients

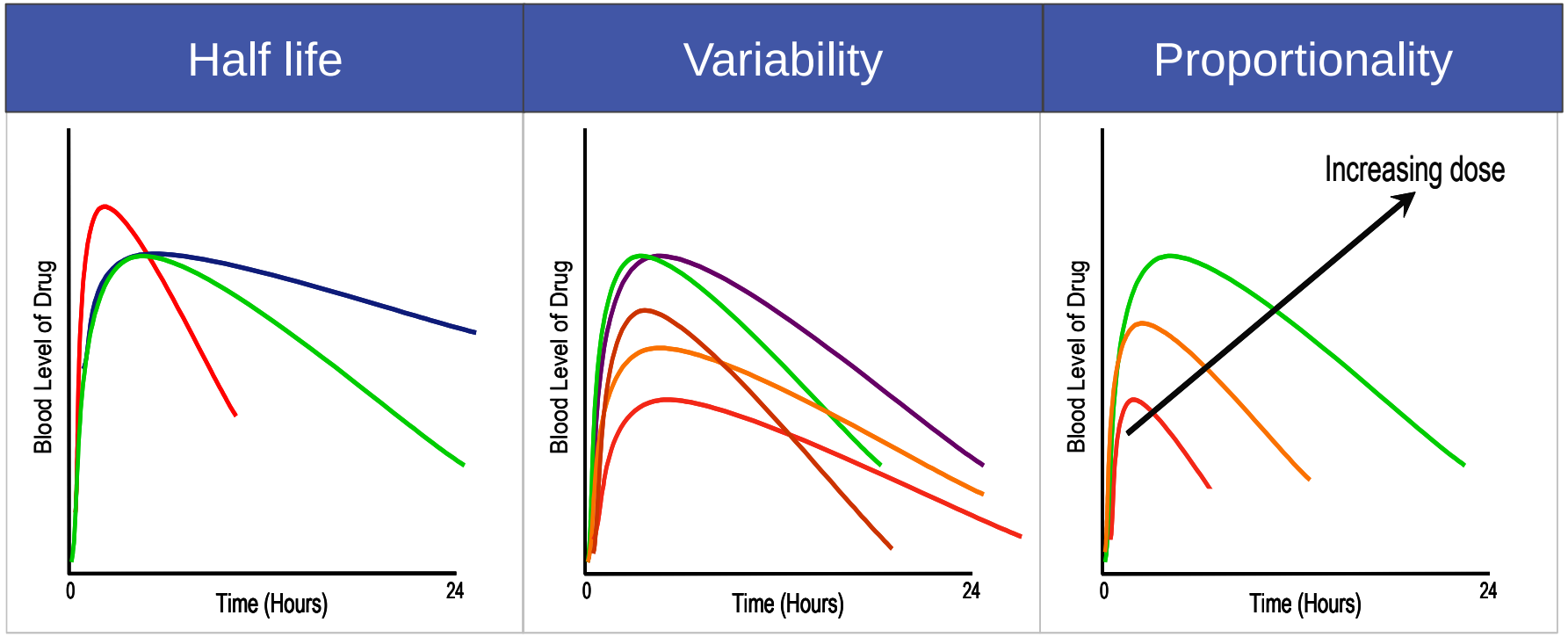


- FIH study performed in healthy volunteers with MEI-401, an oral Pi3kδ inhibitor
- 3 capsule formulations developed and prioritized for evaluation
  - Powder blend; lipid suspension; spray dried dispersion
- Precise unit dose adjustments during SAD
- Blood samples taken to assess target inhibition (basophil activation)
- Drug product suitable for patient trials identified
- Time from initiating CMC activities to patient supply: 12 months
- Positive Phase II data announced at ASCO 2018

Maximising the adaptive nature of Phase I studies

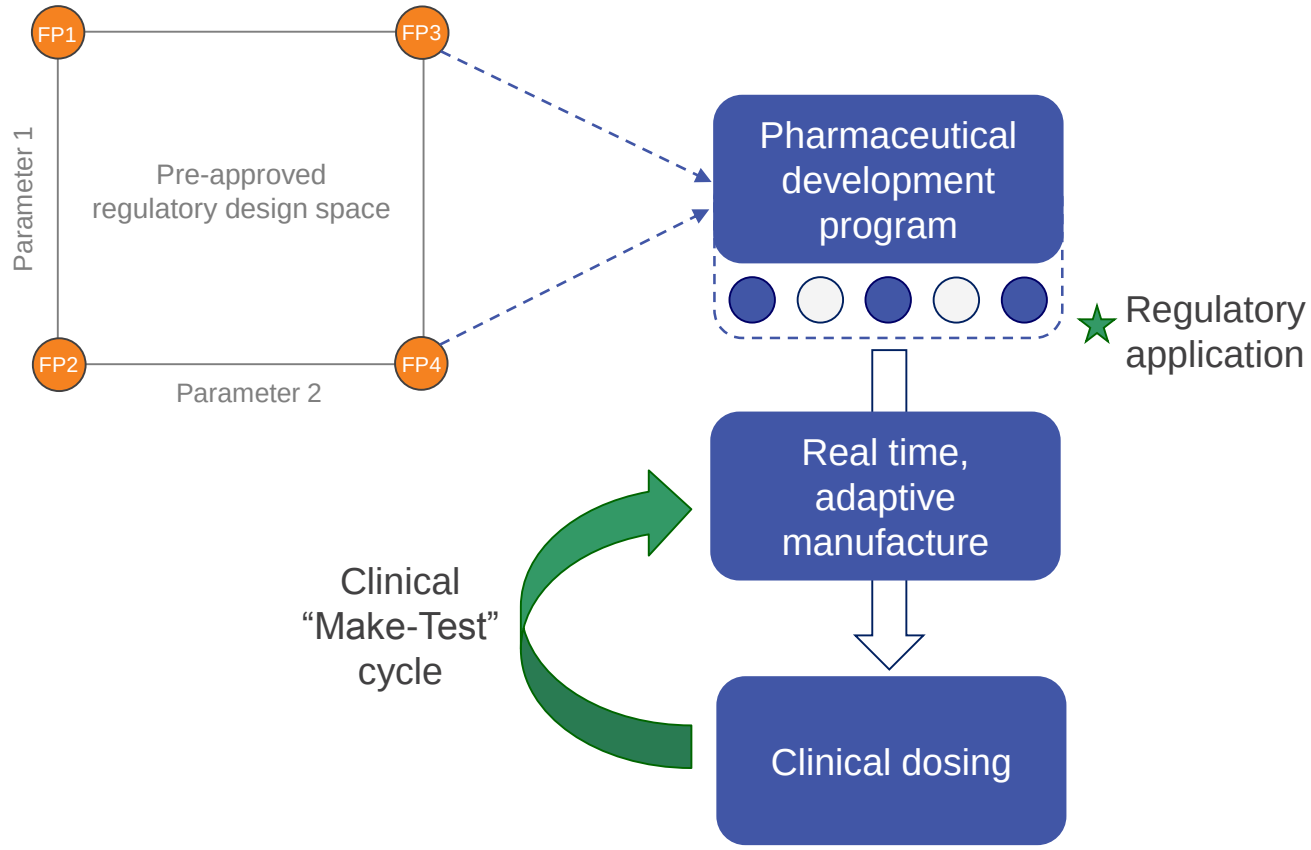
Re-engineering product optimisation

Sub-optimal PK profiles



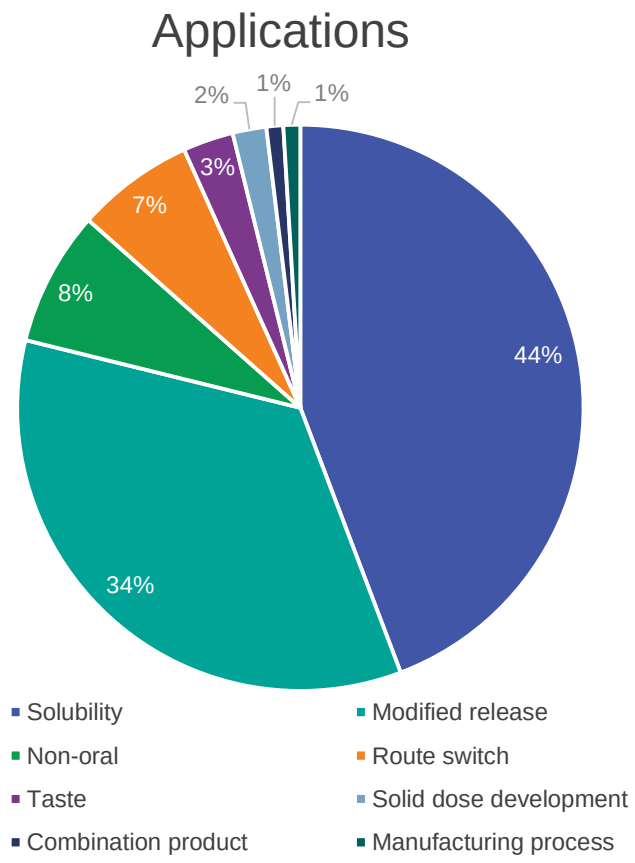
- Not to mention……
  - Poor exposure
  - Positive or negative food effects

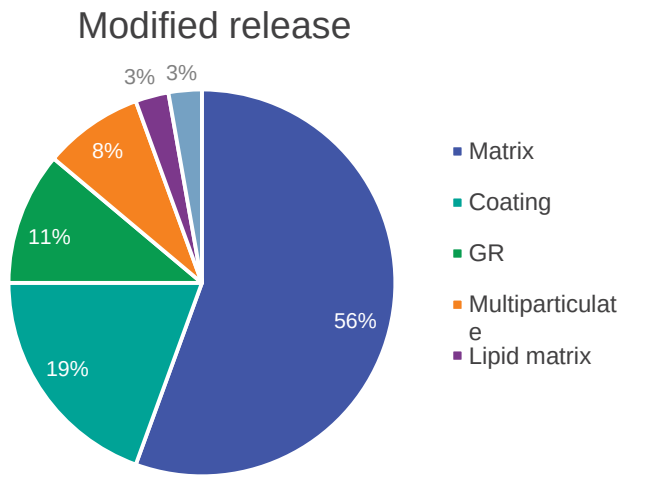
Adaptive programs with real-time formulation flexibility

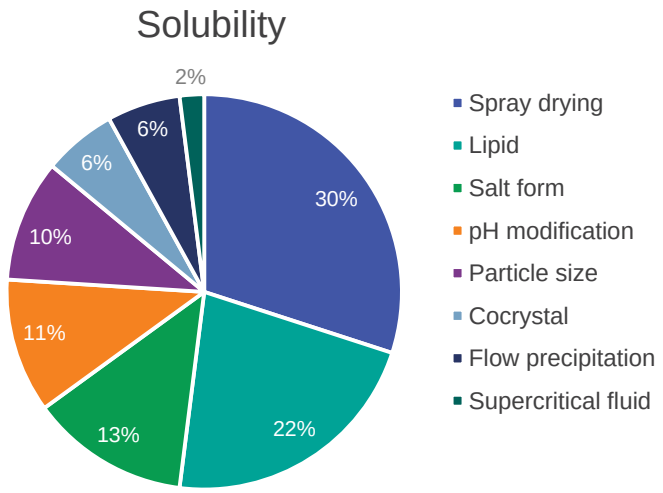


Rapid *F*ormulation development *A*nd *C*linical *T*esting

>150 programs and >500 formulations







Case study:
Optimisation of a controlled release product with targeted GI delivery

- Problem Statement:
  - LY545694 had demonstrated successful POC
  - Short half-life, dose limiting AEs and absorption limited to the small intestine
  - Initial controlled release (CR) formulation developed, but resulted in significant defecation of drug and a subsequent impact on cost of goods

- Target Product Profile:
  - Improved CR formulation to deliver all drug within the target region
  - Achieve equivalent exposure profile
  - Reduce dose and cost of goods

Pharm Res
DOI 10.1007/s11095-012-0798-1

RESEARCH PAPER

Optimization of LY545694 Tosylate Controlled Release Tablets Through Pharmacoscintigraphy

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ABSTRACT

Purpose To optimize a controlled release (CR) matrix formulation with two goals: (1) effectively deliver a prodrug to a preferred absorption region of the upper GI tract, and (2) afford a PK profile similar to a "reference" CR formulation.

Methods A pharmacoscintigraphic clinical study was conducted using a flexible formulation design space. A six-arm, three-prototype study was employed to cover the formulation design space and assess performance against the reference formulation. Pharmacokinetic and scintigraphic data from the first three dosing arms were used to select prototypes to be dosed in subsequent arms.

Results Of three prototypes tested, the third prototype had an optimal release rate. The *in vivo* erosion rate was observed via scintigraphy to reach 90% in 3 h. The AUC ratio relative to the reference for the prodrug was 1.25, while the C_{max} ratio was 1.07. The ratios for the active moiety were 1.31 (AUC) and 1.01 (C_{max}).

Conclusions A single pharmacoscintigraphic study efficiently investigated a wide formulation design space and precisely optimized the release rate with few formulation iterations. The selected formulation provided the desired exposure at a 30% lower dose. The approach is beneficial when drug absorption is limited to a region of the GI tract.

KEY WORDS absorption · controlled-release · flexible design space · pharmacokinetics · prodrug

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INTRODUCTION

LY545694 is an ester prodrug that is primarily hydrolyzed by carboxyesterases (present in the small intestine, blood, and liver) to the active moiety, Compound 645838, a potent and selective ionotropic glutamate receptor antagonist identified as a potential treatment for the management of persistent pain. The structures of each compound are illustrated in Fig. 1. Due to the low permeability of Compound 645838, LY545694 was developed to enhance the oral bioavailability and systemic exposure of Compound 645838. The solubility of LY545694 is ~0.4–0.8 mg/mL across the physiologic pH, with two pk_a values at approximately 3.5 and 8.6. Initial Phase 1 studies of LY545694 as immediate-release formulations (solution and capsules) indicated a short terminal half-life for LY545694 (mean range: 0.72 to 4.5 h) and Compound 645838 (mean range: 2 to 3 h). Dose-limiting adverse events were gastrointestinal (GI) related symptoms such as loss of appetite, nausea, and vomiting. The timing of the adverse events suggested that they might be associated with the maximum plasma concentration of either LY545694 and/or Compound 645838 (mean range of t_{max}: 0.67 to 3 h). Given the desire to modify the concentration-time profile of LY545694 and Compound 645838 to reduce C_{max} and provide the targeted exposure for an extended period of time that would permit a once or twice daily dosing regimen, controlled release (CR) formulations were investigated.

Initial efforts investigated LY545694 CR tablet formulations having the same dosage strength but exhibiting three different *in vitro* release rates: fast, intermediate, and slow release to achieve 80% release in 3, 8–10, and 14 h, respectively. A pharmacokinetic (PK) study in healthy volunteers with these 3 CR formulations demonstrated that the CR formulations allowed for a twice-daily dosing regimen of

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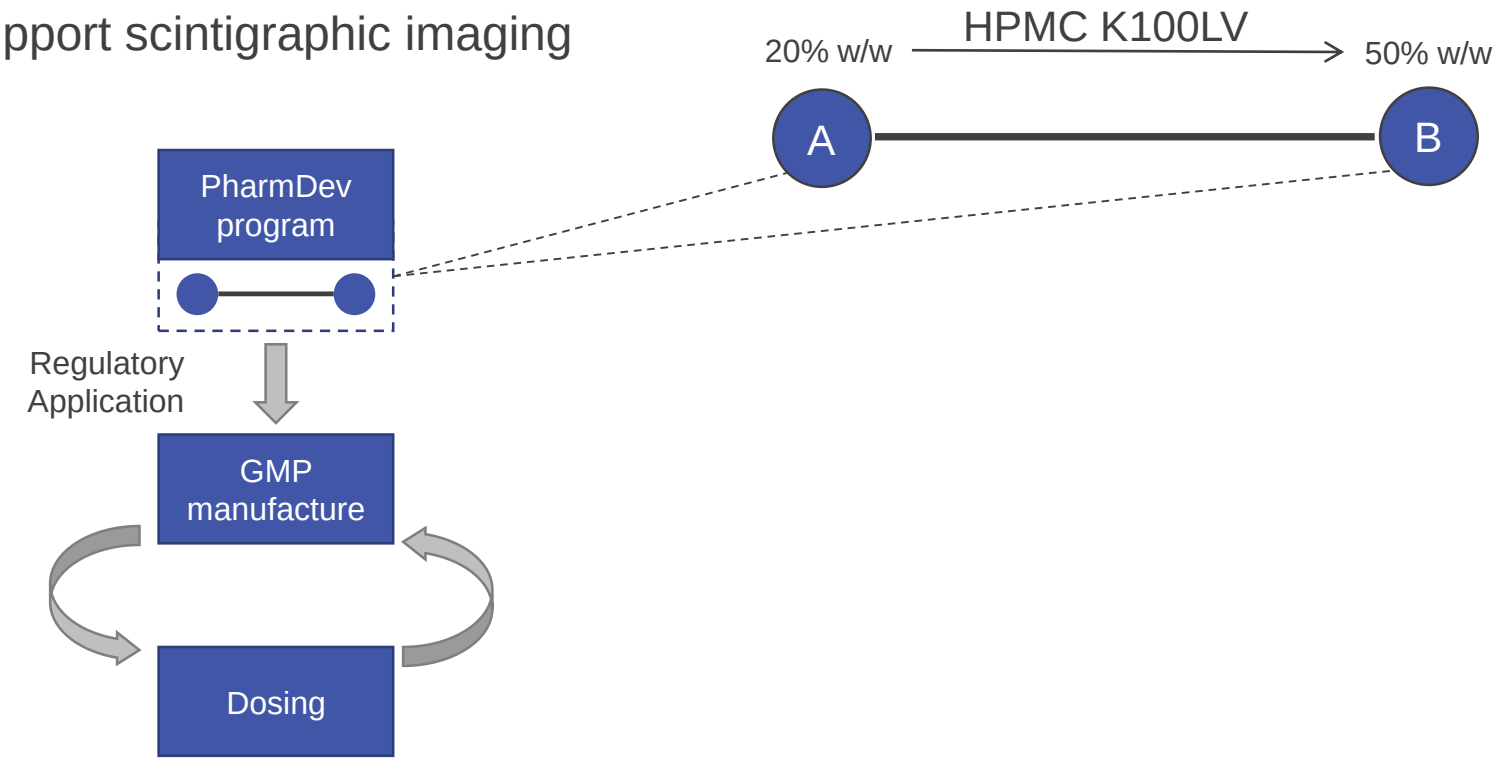
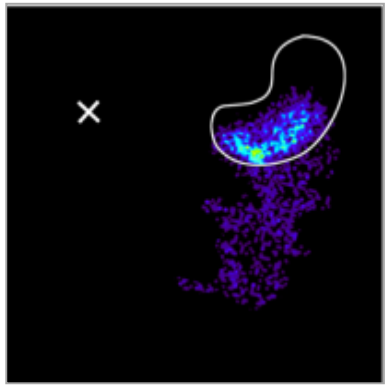
Pharmaceutical Science strategy

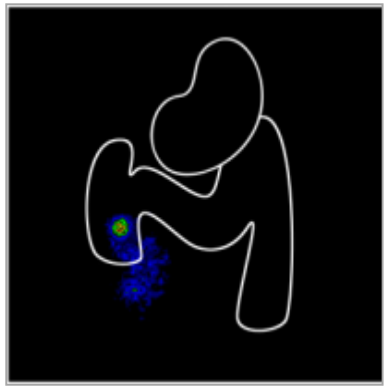
- New CR formulation developed with lower viscosity HPMC
  - Variable release rate achieved via adjustment in polymer composition
  - Reduced dose of 25mg
  - Formulations radiolabelled to support scintigraphic imaging



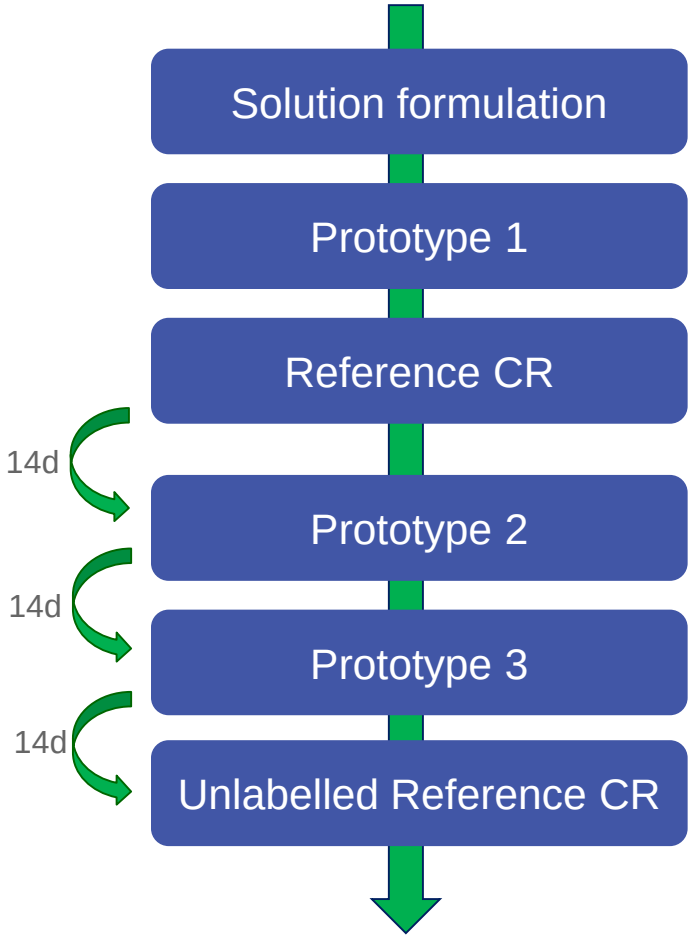
Scintigraphic Imaging

- Gold standard technique for over 40 years
- Gamma emitting radionuclides used to label the formulation
  - Short half-life
  - Low radiation doses
- Images are captured using a gamma camera
  - Non invasive
  - Short imaging times
- Visualise and quantify formulation performance
- Performed in conjunction with PK assessments



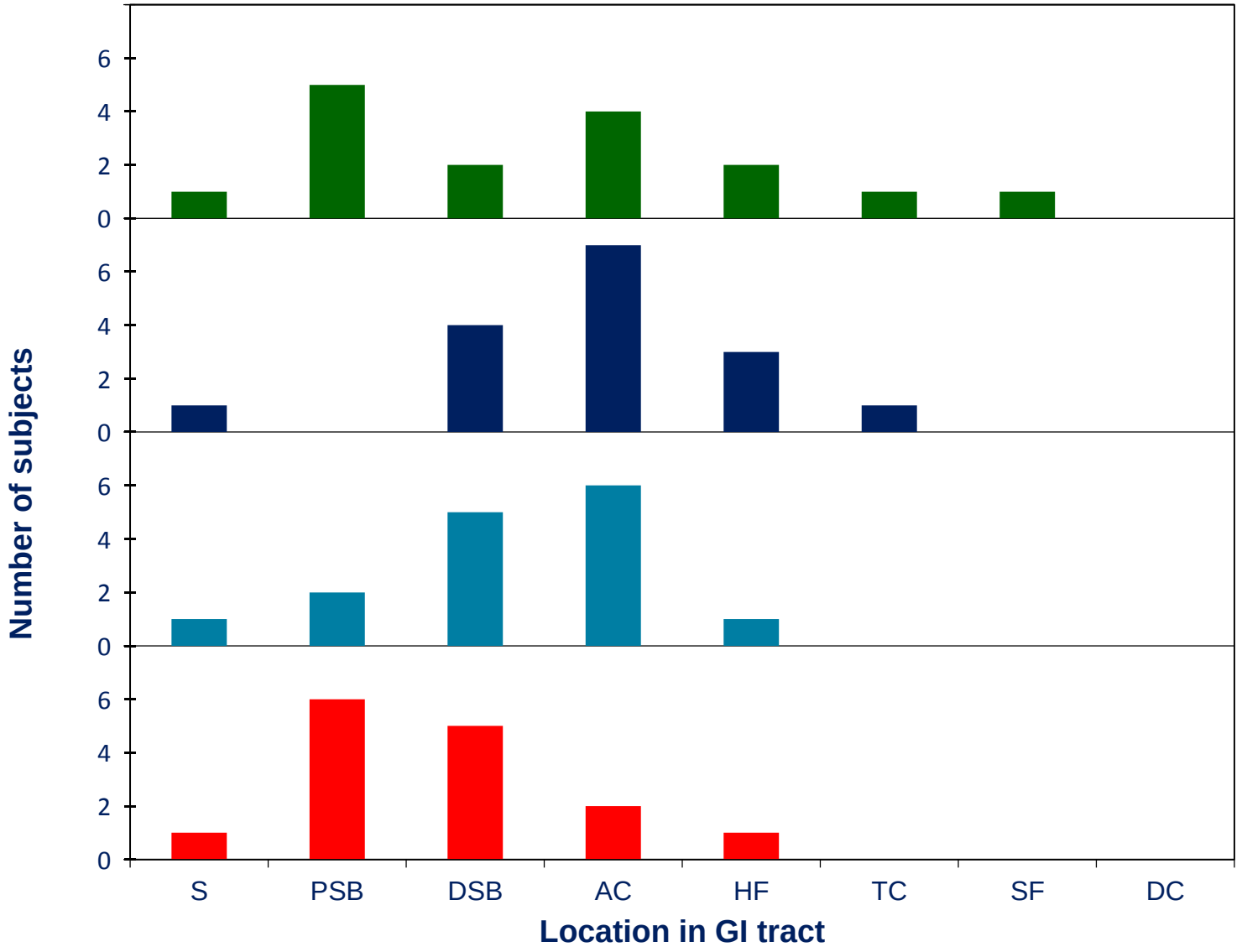


Clinical study design



- Crossover study in 16 healthy volunteers
- 3 formulation prototypes studied
  - Provided opportunity to select products in response to emerging data
  - Prototype 1 selected to contain 30% Methocel K100LV based upon in-vitro data
- Data compared to oral solution and Reference CR products
- Interim decisions made based upon:
  - Scintigraphic imaging data
  - Pharmacokinetic data

Anatomical location of complete erosion



Reference CR tablet

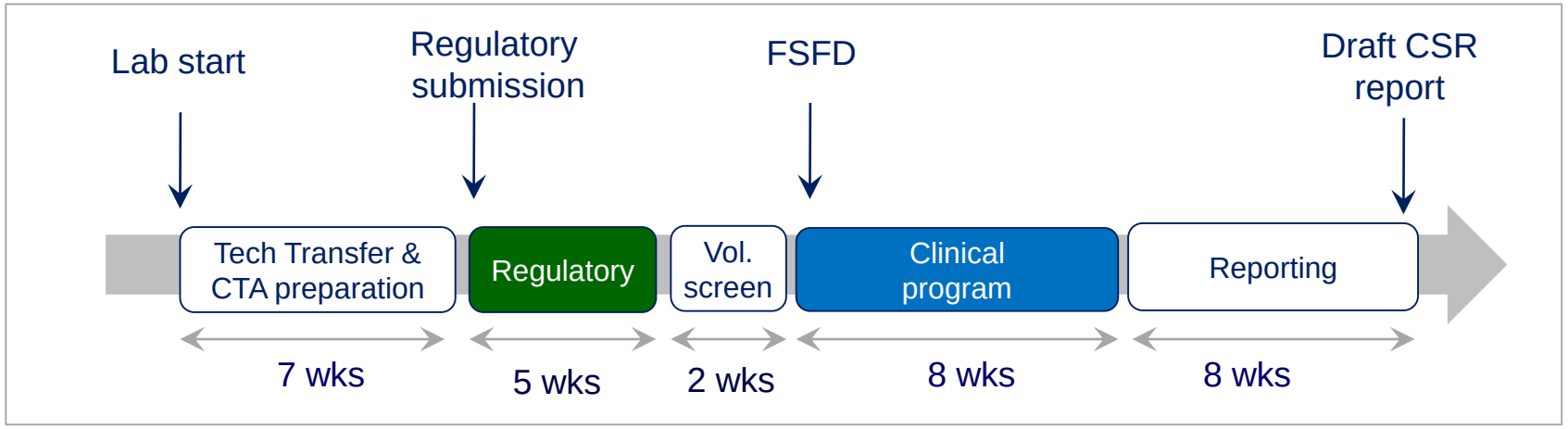
Prototype 1 30% HPMC

Prototype 2 24% HPMC

Prototype 3 20% HPMC

MR formulation optimisation - outcomes

- Study decisions driven by an understanding of the drivers impacting on formulation performance and PK variability
- Efficient delivery of LY545694 to the site of absorption resulted in 30% higher relative bioavailability
- Prototype 3 was selected for further development
- Timeline to completion <8 months



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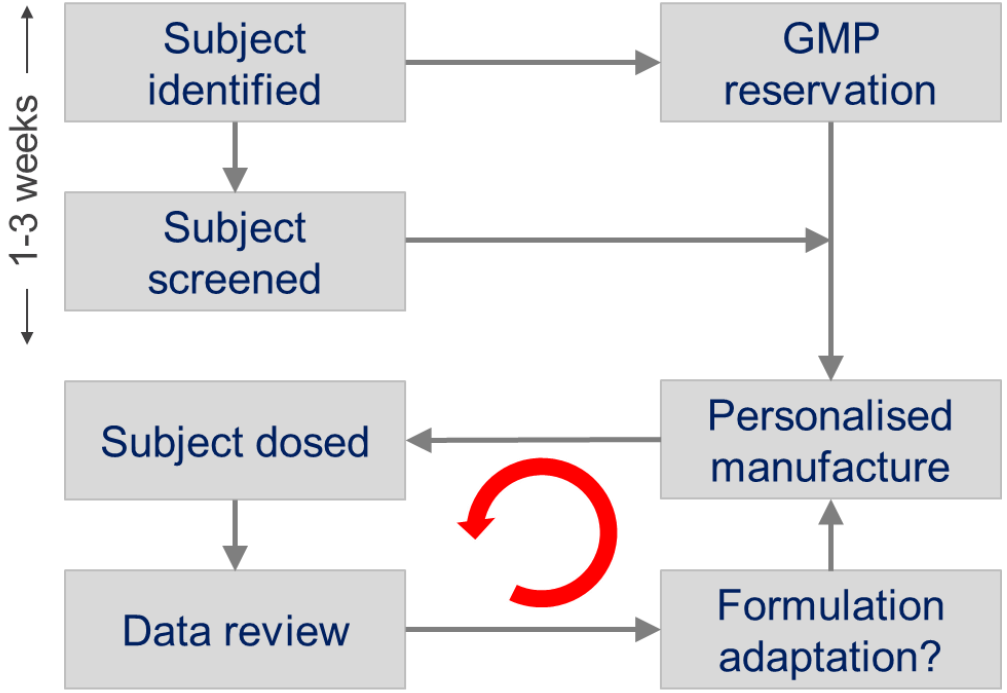
Maximising the adaptive nature of patient studies

Re-engineering supply chains

Drug product supply: challenges and solutions

- Typical challenges
  - Challenging / sporadic patient recruitment
  - Multiple sites / countries
  - Patient weight variability requiring dose flexibility
  - Formulation stability may be limited
  - Small batch size requirements
- Conventional supply chains may not be flexible to meet these needs
- Real-time adaptive GMP manufacturing offers a unique solution….



Case study: real-time adaptive GMP manufacturing and supply

Proof-of-concept in Alagille Syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC)

Program requirements/challenges:

- Pediatric patient population
- Solution formulation, limited stability
- Patient packs required for home dosing
- Recruitment sporadic and unpredictable (n=1)
- Patients dosed based upon body weight
- Dose varies during treatment (fixed volume)
- Dose adjustment in response to emerging data

Program design:

- Randomized and blinded design
- On demand, personalized drug product supply
- GMP manufacturing, labelling and packaging
- QP released and shipping
- Supplied up to 124 weeks for daily dosing
- Resupplied every 1-3 months
- >180 patients, >1300 shipments
- >25 sites across 8 countries

Product available for dosing globally within 1-3 weeks of confirmed subject eligibility

Summary

- Integrated and adaptive Phase I protocols are the established norm
  - Does this alone adequately address today's challenges in early drug development?
- Opportunities are presenting from Translational Pharmaceutics
  - Integration of GMP manufacturing and clinical testing
  - Using clinical data to drive formulation decisions
- Adaptive clinical trials today
  - Adaptive protocols and adaptive drug products
  - More informed, faster and cost-effective decision making
  - Maximised potential for success
- Industry is adopting this approach
  - >80% of studies at Quotient benefited from Translational Pharmaceutics (2012-17 data)

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