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

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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 today's 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
Getting the product to the patient

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

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

The integration of formulation development, real-time adaptive GMP manufacturing and clinical testing
Transforming development into “make-test” cycles

Day 1-3
- Dose
- Residency
- Safety, PK & PD

Day 4-6
- 72h bioanalysis

Day 7
- PK parameter estimates

Day 8
- Interim decision meeting
- Safety/PK report reviews
- “What next” decision

Day 9-13
- GMP manufacture/release of selected drug product
- Transfer to clinical unit

Day 1 - 3
- Dose
- Residency
- Safety, PK & PD
## Benefits to industry, regulators and patients

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

First-in-human to proof-of-concept

Candidate selection ➔ Preclinical ➔ Early development ➔ Late development ➔ Commercial

Formulation optimization
Life cycle management

RapidFACT®
(Rapid Formulation development And Clinical Testing)
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?

- Healthy volunteer (SAD)
- Healthy volunteer (MAD)
- Patient (POC)

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

- Solution/Suspension
- Solid dosage form

* 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

Diagram:

- Formulation strategy
  - Minimise investment until POC
  - Significant investment prior to FIH
  - Switch to solid between studies via BA

- SAD
  - Drug/Powder in bottle/capsule

- MAD
  - Formulated solid dosage form

- POC
  - D/P in B/C
  - Solid dosage form

- Phase II
  - Late switch to solid delays PhII
  - Swift transition to PhII
  - Phase I duration extended

Phase I duration extended
Real-time manufacture within a FIH program

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
- 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
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

Selection of Formulation 1, 2 or 3 for progression
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 Formulation development And Clinical Testing
>150 programs and >500 formulations

Applications
- Solubility: 34%
- Non-oral: 7%
- Taste: 8%
- Combination product: 3%
- Modified release: 1%
- Route switch: 2%
- Solid dose development: 1%
- Manufacturing process: 1%
- Other: 2%

Modified release
- Matrix: 56%
- Coating: 19%
- GR: 8%
- Multiparticulate: 11%
- Lipid matrix: 10%
- Other: 3%

Solubility
- Spray drying: 22%
- Lipid: 13%
- Salt form: 6%
- pH modification: 11%
- Particle size: 10%
- Cocrystal: 22%
- Flow precipitation: 6%
- Supercritical fluid: 30%
- Other: 2%
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 within the target region
  - Achieve equivalent exposure profile
  - Reduce dose and cost of goods
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

Number of subjects

Location in GI tract

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
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)