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Adaptive manufacturing: a new paradigm to improve efficiency and effectiveness in early oncology development

QUOTIENT CLINICAL
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INTRODUCTION

The application of genomics and proteomics provides personalised approach to drug discovery and development, enabling the targeted evaluation of emerging therapeutics in specific patient sub-populations with oncology. Coupled with problematic recruitment rates, prolonged study durations and the potential need to continue treatment if a positive clinical response is observed, this can raise real challenges to ensure the right drug product is available at the right time for each individual patient.

Conventional drug product manufacture and supply chains are not effectively configured to address these growing challenges and given the increasing industry focus on oncology there is an unmet need in the industry for a more efficient and flexible approach to provide drug product for these early clinical studies.

Presented here is an innovate approach to overcome these challenges by utilising a **real-time, adaptive manufacturing and supply** platform.

Example scenarios of where this new approach is most impactful include:

- Dose escalation algorithms in the First-in-Human / Patient (FIH/P) study
- Evaluation of improved formulations to address sub-optimal pharmacokinetics (PK)
- Conduct of regulatory ADME mass balance study [1]

METHODS

Translational Pharmaceutics™ is a validated platform [2] which integrates pharmaceutical development and GMP manufacture with co-located clinical conduct on a single site.

- Drug product is manufactured at small scale, under GMP conditions, immediately prior to dosing
- Minimal stability data are required to support clinical dosing (2-14 days)
- Only drug product required for dosing is manufactured
- Real time decisions are made on the basis of emerging safety, PK and PD human data

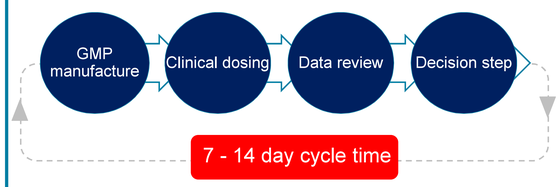

Figure 1: Clinical "make and test" cycles

	Conventional Process	Translational Pharmaceutics
Timelines savings	None	>6 months
Flexibility	Low	High
Drug substance consumption	100%	<15%
Vendor management	Multiple	Single

Table 1: Proven benefits of Translational Pharmaceutics

Using the principles established for onsite dosing in healthy volunteers. this platform has now been extended to allow drug products to be manufactured 'on demand' and supplied to oncology patient studies at specialist clinical units.

This allows a fully flexible and adaptive manufacture and supply program which reacts in response to patient needs and recruitment timelines.

By integrating the pharmaceutical development, GMP manufacturing and patient supply activities, customized drug product can be supplied to specialist clinics globally within 2-3 weeks of notification of patient availability.

It also allows formulation compositions and batch sizes to be adjusted in 'real time' in response to emerging data.

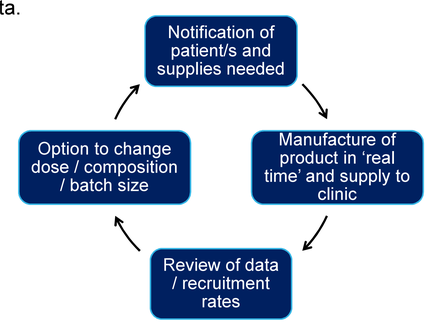

Figure 2: Real-time adaptive manufacture and supply paradigm

Case Study 1:

Drug X, a molecular targeted molecule, was to be tested within a Phase I dose escalation study. A standard 3+3 design was to be utilised with multiple clinics open for enrolment within Europe.

The clinical product consisted of an enteric coated immediate release tablet.

A flexible CMC program was designed and regulatory approval sought to support the study (Table 2).

Conventional Process	Translational Pharmaceutics (real-time adaptive manufacturing)
Single composition, dose and batch size (large)	"Manufacturing space" established - bracketed dose strength - Flexible manufacture scale
Long term stability program - 12-18 months shelf life	Shorter stability program - 6 months shelf life
Single batch manufactured at scale at start of study	'On demand' batches (flexible scale) manufactured in real time
Limited to no flexibility to increase/change dose	High flexibility to react to recruitment, patient needs and emerging data

Table 2: Comparison of Convention vs Translational Pharmaceutics for Phase I supply

The manufacture design space was utilised to enable flexible resupply based on on-going recruitment rates and emerging data. A make-supply cycle time of 15 calendar days was established.

Case Study 2:

Drug Z, an intravenous cytotoxic molecule in late Phase II trials required a regulatory mass balance and metabolism study to be conducted. Due to the toxicity of the drug the only viable option was to dose in patients.

Key challenges for these study types are the;

- Stability limitations for ^{14}C APIs and ^{14}C drug products
- Lack of predictability in patient identification
- Batch sizes given limited API availability

By using the new manufacture and supply platform these hurdles were overcome as shown in Table 3. The CMC development program supported a personalised 'per patient' manufacture process for the IV product required in this study.

Conventional Process	Translational Pharmaceutics (real-time adaptive manufacturing)
12 month's stability needed for ^{14}C API	Still 12 months because this is driven by patient recruitment
12 months stability needed for drug product - full ICH stability program	7 days for oral or parenteral products
Drug product batch size – in excess given conventional CMO set up	'Per patient' batch sizes can be manufactured to full GMP

Table 3: Comparison of convention vs Translational Pharmaceutics for ADME patient supply

Regulatory data for the IV solution was collected using unlabelled API within 6 weeks from project initiation. A 7 day shelf life was applied to the product to support the study.

An aseptic process validation and radiolabelled trial were also performed prior to the clinical manufactures to provide supporting regulatory quality assurance data for the process and product.

Product was manufactured in real-time under GMP upon notification of each patient being enrolled. The IV product was manufactured, QP released and shipped to a specialist European clinic for dosing within 5 days of notification.

RESULTS

Case Study 1 – deliverables:

- Deferred investment in API and product manufacture until recruitment rates understood
- Minimal wastage as only product quantities needed for dosing were manufactured
- Program conducted on reduced stability due to 2-3 weeks supply of product when required
- Different doses manufactured based on emerging data

Case Study 2 – deliverables:

- Significant reduction in ^{14}C API and drug product wastage due to 'per patient' manufactures at small scale
- Reduced time and cost in development program by minimal stability and shelf life requirements
- Personalized manufacture of GMP drug product

CONCLUSION

Translational Pharmaceutics now enables a real-time adaptive manufacture approach for early development studies in oncology patients. Demonstrated benefits include:

- Reduced timelines to clinic
- Reduced drug product stability requirements
- Increased efficiency of drug substance consumption
- Flexibility for 'In study' adjustments to drug product dose/scale

This new CMC paradigm is ideally suited to the clinical development of personalized medicines.

REFERENCES

1) Clarke-Lens et al 'Flexible Strategies for the Conduct of Human Metabolism Studies with Oncology Molecules', ISSX 2014
2) Scholes et al 'Translational Pharmaceutics - Interactive Drug Development to Enable Rapid Optimisation of Drug Products in Early Development', AAPS 2009