Reference W4359

Real time adaptive manufacturing - a new paradigm for personalized drug products in clinical development

QUOTIENT CLINICAL
The Translational Pharmaceutics Company

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PURPOSE

The emergence of personalized and patient-centric medicine presents an exciting proposition for improved therapeutic outcomes. Using a pharmacokinetic (PK) analogy, the goal is to ensure the right drug product is available for the right patient at the right time. There are several instances where the ability to tailor a formulation to unique, individual patient needs would be highly advantageous, whether dictated by genetic factors or subject preference (Table 1):

Table 1: Example Drivers for Personalization of Medicines

Requirement	Driver
Customized dose selection	Subject body mass or surface area
Optimized treatment regimens to maximize efficacy and minimize adverse events	Pharmacogenomics-driven screening of subjects via molecular or genetic diagnostics to identify metabolic polymorphism
Stratified treatments	Disease biology and target receptor expression
Patient-centric formulation acceptability	Palatability and compliance for oral pediatric treatments

Within this model however lies a significant challenge for conventional drug product manufacturing and supply processes, historically geared to providing fixed, commoditized formulations in both clinical trial and commercial settings. Cycle times and production costs are prohibitive for the rapid, flexible manufacture of drug products tailored to individual patient needs (Table 2). As such this "one size fits all" model presents an increased risk of sub-optimal trial outcomes and even failure to meet key study endpoints or demonstrate proof-of-concept (PoC).

Table 2: Comparison of conventional and future drug product supply paradigms

Parameter	Conventional model	New requirements
Batch sizes	Large	Flexible/personal
Product customization	None	High
Lead times	Long	Short
Responsiveness	Low	High
Shelf-life	>12months	Flexible

These challenges are further magnified in many of today's key areas of clinical research such as oncology, orphan diseases and pediatric medicines where protracted and unpredictable recruitment rates place further demands on development and implementation of flexible CMC strategies.

Here we report on a new real-time adaptive GMP manufacturing paradigm serving patient and study needs by delivering personalized drug products on demand.

METHODS

Translational Pharmaceutics®, the integration of formulation development, GMP manufacturing and clinical testing, is a proven approach to reduce the time and cost in early clinical development. Drug products are manufactured in real-time immediately prior to dosing, thereby enabling flexibility in formulation composition for the next study period based on arising clinical data (safety, PK or pharmacodynamic (PD)) from the previous one[1].

These principles have now been extended from the conduct of healthy volunteer studies in an integrated GMP production and clinical pharmacology unit (Figure 1), to the real-time manufacture and supply of products for patient trials on a global basis.(Figure 2)

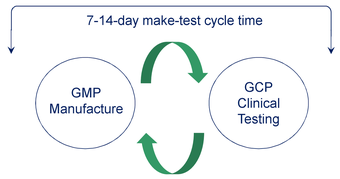

Figure 1: Make and test cycle for Phase I volunteer studies

The development and implementation of a per-project supplies response system allows for drug product requests to be made based on individual patient criteria. A personalized formulation is immediately manufactured for dosing under the auspices of the approved clinical protocol and regulatory submission. Products are released with full on-site Quality Control (QC), Quality Assurance (QA) and Qualified Person (QP) oversight prior to immediate dispatch via courier to the clinical site.

Three case studies are described where applications of this capability has been pivotal in the conduct of clinical pharmacology, PoC and pivotal efficacy studies in various patient populations.

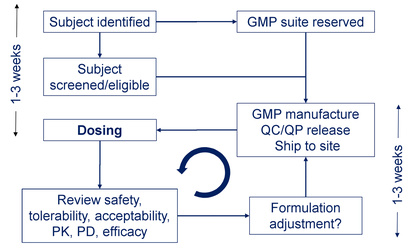

Figure 2: Make and supply cycle for patient studies

RESULTS AND DISCUSSION

Case study #1:

Orphan disease PoC study[2]

- Healthy volunteer single and multiple ascending dose study completed at Quotient Clinical, UK
- PoC study conducted at 5 specialist key opinion leader (KoL) clinical sites in Germany (Figure 3)
- Continuity of drug product supply (lipid formulation in hard shell capsule) from Quotient Clinical to KoL sites monthly based on patient recruitment rates
- 14d notice period covered GMP manufacture, QC/QP release and shipping of patient packs to clinical site
- Drug substance consumption and product shelf-life optimized

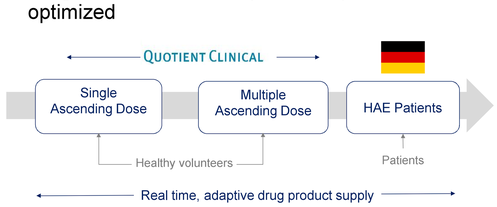

Figure 3: Integrated FIH-PoC program with continuity of drug product supply

Case study #2:

Clinical ADME study in oncology patients[3]

- Cytotoxic drug (vosaroxin) not amenable to healthy volunteer dosing requiring conduct of regulatory mass balance study in patient population
- Recruitment of n=6 subjects expected to be sporadic and protracted (>12 months)
- Intravenous ^{14}C drug products manufactured and released on per-patient basis, based on subject body weight
- Product dosed in the Netherlands within 1 week of manufacture in the UK

Figure 4: Real-time adaptive manufacturing for oncology ADME patient study

Case study #3:

Pivotal global pediatric studies in rare liver disease

- Novel therapy for Alagille Syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC) requires dose to be based on (i) body weight, (ii) phase of treatment and (iii) therapeutic response
- 6 studies with initial and repeat supplies required for treatment periods of up to 104 weeks
- Randomized and blinded study design
- Personalized solution formulations and patient packs manufactured, labelled, released and supplied on demand for home dosing
- Drug products manufactured, released and shipped within 7-10 days of notification, arriving at global study sites within 1-3 days
- >500 products manufactured for >150 patients in >10 countries at >20 recruiting sites
- >99% on time dosing

CONCLUSIONS

The advent of personalized medicines and pharmacogenomics is creating a requirement for on demand manufacture of customized drug products, uniquely focused around individual patient needs. The established principles of Translational Pharmaceutics can be applied for the real-time adaptive manufacture and supply of formulations on a global basis.

Personalized GMP drug products can be made available for dosing within 1 to 3 weeks of request, independent of formulation type and geography.

Such capabilities will have increasing applications as disease treatment becomes more patient-centric, to administer the optimum drug product based on individual demographic and genetic profiles, improving outcomes.

REFERENCES

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