



Accelerating the development of orphan drugs for rare diseases



Introduction

A rare disease is defined as one affecting less than 200,000 people (in the US) or no more than five in 10,000 of the general EU population^{1,2}. There are approximately 7,000 rare diseases, affecting an estimated 30 million people in each of the US and EU. Worldwide there are over 300 million people living with one or more identified rare diseases representing 3.5% - 5.9% of the global population³. The development of new treatments to address these unmet clinical needs clearly represents an important global health priority.

Historically commercial pressures meant the challenges and cost of developing such medicines were not cost-effective given the projected financial returns. In recent years however there has been a sea change in industry activity as evidenced by the increasing prevalence within drug development pipelines and the numbers of new molecules reaching the marketplace. Between 2016-2019, 82 of the 175 new FDA approvals were for rare diseases. Regulatory authorities have sought to encourage and motivate industry to develop drugs for these serious medical conditions through the creation of a supportive infrastructure (Table 1). As well as an interactive and collegiate development pathway, the incentive of market exclusivity has also been key, with protection for 7 years in the US and 10 years in the EU being assured. In Europe an additional 2 years is also granted in the case of pediatric disease. It should also be noted that many orphan products will also have additional regulatory designations to support expedited development and early access for patients.

These designations are typically assigned for serious or life threatening diseases and/or where there are unmet medical needs and in the US include:

- > Accelerated approval
- > Breakthrough designation
- > Fast track designation
- > Priority review

Nevertheless, despite improvements in regulatory support and commercial rewards, in comparison to more widespread diseases difficulties remain for drug developers in bringing these products to market. R&D budgets are increasingly constrained, product development will be (at least) as challenging, clinical recruitment and research will be problematic in rare patient populations, and reimbursement negotiations with authorities will undoubtedly be emotive.

This white paper will discuss four principal CMC challenges for the developers of orphan drugs, and the potential solutions which are emerging:

- > Development of patient-centric dosage forms based upon molecule properties and patient needs
- > Rapid accelerated optimization and validation of product performance in humans
- > Tailored manufacturing and supply of drug products into patient trials
- > Rapid scale-up and commercial manufacturing of low-volume products

>50

Quotient Sciences have supported over 50 development programs for rare disease in the past 5 years

Table 1: Regulatory support for the development of orphan drugs for rare disease.

	US / FDA	EU / EMA
Market exclusivity	> 7 years	> 10 years
Licence applications	> 90-day review timelines	> Centralized procedure
Development support	<ul style="list-style-type: none"> > Tax credits of 50 percent for expenses incurred during clinical research and testing > Orphan product Grant program 	<ul style="list-style-type: none"> > Protocol assistance > Administrative and procedural assistance for SMEs
Fees	> Waive prescription drug user fees	> Fee reductions

Formulation development

Formulation development of orphan drugs often requires a “non-traditional” approach for several reasons. Active pharmaceutical ingredients (APIs) may be expensive and only available in limited amounts only due to small(er) scale syntheses. Early preformulation and formulation development studies must therefore be carried out with even greater efficiency to maximize the characterization and understanding of the API’s physicochemical and biopharmaceutics properties. A focus needs to be on the critical data which will inform formulation selection and robust formulation design. Minimizing formulation development time will also be of the essence given the aforementioned desires to accelerate molecules to patients. Speed should not compromise quality however; incomplete or erroneous initial formulation development work whilst providing a quick start has potential to delay the program significantly downstream, through sub-optimal clinical data or during process scale-up. An overarching theme will also be the need to carefully manage R&D expenditure due to commercial pressures and potential.

In the orphan drug space, Quotient is acutely aware of the need to “start with the end in mind” in terms of defining a target product profile, designing early experiments to balance both a rapid entry to clinic, but not at the risk of creating product stability or scale-up challenges downstream which could cause significant program delays. Our approach has been to prioritize the key API characterization data required, which allows our scientific experts to recommend selection of the appropriate API form as well as informing a data-driven strategy for preclinical and clinical pharmaceutical development. Formulation strategies are informed by the Developability Classification System (DCS), which

is particularly important in teasing apart dissolution or solubility limited API risks for drug absorption, to direct the selection of enabling technologies⁴. With biopharmaceutics experience and knowledge from having performed over 1500 Phase I clinical trials, we can factor in and anticipate clinical considerations not just based on the in vitro performance of pharmaceutical formulations. Early laboratory prototyping is performed on bench scale equipment which mirror both small scale and mid-to-large scale GMP manufacturing, to de-risk process scale-up and development should the molecule achieve its early clinical endpoints. At Quotient, we emphasize the importance of data driven decisions in early development.

Another reality of rare diseases is that many will be prevalent in the pediatric population, raising the additional requirement for the development of age-appropriate and palatable dosage forms. Regulatory guidance provides industry with clear direction on this^{5,6}. Pediatric formulations require specialist knowledge given the need to carefully select a technology platform appropriate for the target age range, the type and levels of suitable excipients, the need to mask any potential aversive properties of the API, and the method of administration and any concomitant dosing aids. Quotient has a wealth of experience in the design and development of pediatric medicines based on these considerations and have worked on all product types, from oral solutions and suspensions, to powders for reconstitution, to granules, sprinkles and mini tablets. Based on the program need, the development of an age-appropriate formulation can also be performed concurrently or sequentially to the adult format.

Clinical development: accelerating to proof of concept

In a market segment where concerns over development time and cost are even more accentuated, the need to manage R&D budgets whilst not compromising speed to market is crucial. As with all programs, successful and early demonstration of clinical proof of concept (POC) in a patient population is a key milestone. How can we therefore implement a lean early development program to achieve this goal, but at the same time not create unwanted barriers or development hurdles to subsequently progress into downstream development? Key to success we believe will be the drug product.

In today's industry pipeline, molecules with challenging chemistry are prevalent across all therapeutic indications. The requirement to overcome poor solubility and bioavailability is as relevant in the development of orphan products as any others. How can we therefore reduce the risk in early clinical research from an under-performing formulation delaying or worse still terminating the program? How can we start the first-in-human (FIH) study with a fit-for-purpose formulation, and continue with one which maximizes the potential for clinical success and has the legs for downstream patient trials? How can we avoid critical path bridging studies, to then supply product seamlessly into the POC patient study?

At Quotient Sciences we have demonstrated the benefits of embedding formulation flexibility within FIH trials to enable a "patient ready" formulation to be identified and be ready for POC studies in an average of 12 months, less than half the time of the industry standard⁷.

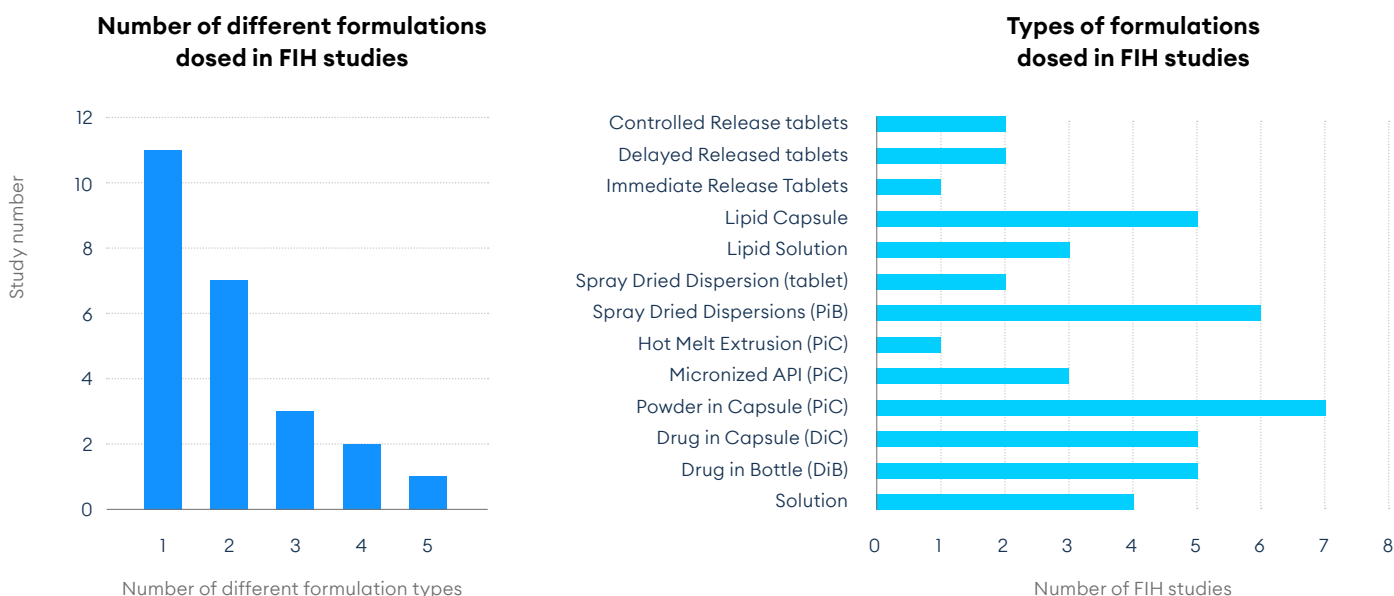
This is accomplished by the close integration of real-time manufacturing and clinical testing, or Translational Pharmaceuticals[®]. With an adaptive drug product strategy and clinical protocol, and using a 14 day "make-test" cycle, formulation decisions can be made on the basis of emerging human data. Within the FIH protocol this enables:

- > Precision in dose escalation
- > Screening of different formulation technologies
- > Bridging from liquid to solid dose formulations

Studies can start quickly with a simple FIH formulation, allowing parallel development of a solid oral format, which can then be introduced into a later part of the FIH protocol without the need for a separate clinical PK bridging study. A summary of recent oral FIH studies is shown in Figure 1 highlighting the breadth of formulation assessments which can be made, and how a preferred formulation type can be quickly identified.

At the end of dosing healthy volunteers in the FIH trial the lead formulation can then be immediately manufactured and supplied into the patient POC study. No further pharmaceutical development or clinical bridging work is required. In some diseases it may be possible to dose a patient cohort within the same protocol depending on clinical endpoints, or focus may switch to a separate multi-national, multi-site study especially if there will be challenges in patient recruitment, even for what can typically be a small cohort of subjects.

Figure 1: Formulation flexibility in recent FIH studies at Quotient Sciences showing (a) number of different formulations dosed per study and (b) formulation types



Case study

An integrated FIH-POC program for BCX4161, a novel treatment for acute hereditary angioedema

BCX4161, a potent small molecule inhibitor of plasma kallikrein, was being developed as an oral treatment to prevent acute hereditary angioedema (HAE) attacks. Based on the molecule's biopharmaceutical properties, a lipid-based hard gelatin capsule formulation was developed with unit dose flexibility of 25-100mg BCX4161 per capsule. Short-term stability data to support a shelf-life assignment of 10 days for the FIH study were generated and included in the regulatory submission. Drug products were manufactured prior to each study period to enable precision in dose

escalation during single and multiple dosing. ICH stability was performed in parallel to support longer-term development. Following successful completion of the FIH program, a 28 day Phase IIa study in HAE patients was immediately initiated. Drug product was supplied monthly based on patient recruitment to six sites in Germany and the UK. Program integration accelerated the timeline to initiation of the POC study to less than 12 months after commencement of the FIH program.

Process development, scale-up & clinical manufacturing for Phase II/III

Clinical manufacturing and supply paradigms

Due to the low prevalence of rare diseases in the general population, patient trials can be extremely challenging to perform. Patient recruitment is likely to be slow and sporadic, which will mean the protracted conduct of studies across multiple sites and countries, stretching potentially over several years. As such, the supply chain for orphan drug programs is complicated based on numbers of patients to be enrolled in the clinical trial, number of countries participating, and the regulatory requirements of those countries. In addition there is also likely to be a greater need for personalization of the product to individual patient needs, for example dose adjustments based on subject age/weight. Quotient has been providing supply chain solutions for orphan projects for over a decade and is perfectly positioned to support complex clinical trials of this type.

Traditional large batch manufacturing of hundreds of thousands of dose units and multiple strengths has its place in the industry. However, are these conventional drug product supply chains properly geared for orphan drug trials which may require small batch sizes, low volume requirement per year and product customization? A new model is needed where the

manufacturing and supply program can be tailored or adapted to the unique needs of each program, to get the right product to the right patient at the right time. As seen in other industry trends, stratified patient populations and product tuning is driving an ever-increasing need for personalization of the drug product.

At Quotient, we provide the full spectrum of manufacturing and supply paradigms, from traditional large batch manufacturing, through bright stock distribution and also personalized manufacturing. Table 2 compares and contrasts the benefits of traditional batch manufacturing with personalized manufacturing. To meet this new patient paradigm for rare diseases, there are compelling drivers for small batch sizes, conservation of API, dose flexibility to meet individual subject needs and reduced stability needs. Fundamentally, with personalized manufacturing, product is made on-demand, only when needed based on patient requirements. Overall this alternative approach offers a reduction in waste and cost, whilst maximizing the potential for clinical success.

Table 2: Comparative benefits of traditional batch manufacturing and personalized manufacturing

	Personalized Manufacturing	Traditional Batch Manufacturing
Batch size	Small	Large
Dose flexibility	High	Low
Labelling / shipping	Per patient/country	Bulk product
Shelf-life / stability	Short-term	Long-term
API consumption	Low	High
Product overage / waste	Low	High
Cost	Low	High

Scale up

Recognizing the need to move rapidly through clinical development, Quotient has the capability to efficiently scale-up drug product manufacturing processes from Phase I to meet the demands of later clinical trial requirements and ensure seamless transition to larger scale manufacturing and drug product commercialization. Underpinning our technical expertise is an organizational design with globally integrated departments and a strong project management capability. This enables seamless progression of manufacturing programs as a molecule transitions through development, with equipment trains for scaling up pharmaceutical manufacturing processes from gram quantities to multi-kilogram batches (e.g. 50 kg).

Our team of dedicated formulation and process experts support the identification of Critical Process Parameters (CPP) to allow a robust scale-up to the required batch sizes. Identifying and understanding the Critical Quality Attributes (CQAs) and CPPs earlier in formulation development is the key for successful scale-up. Quotient also applies the principles of Quality by Design (QbD)

in formulation development to systematically understand the relationships between formulation and process “inputs” and product quality and performance “outputs” to define in-process controls, product specifications and hence the “safe space” for future operations. QbD and design of experiment (DoE) approaches are implemented to help ensure the development of robust processes and methods. Formulation prototypes are stressed early on in order to predict long term stability to avoid any surprises in the program.

Our biopharmaceutics experts will also stay connected to the project as the molecule and product moves from early development to late-stage. As a result, with no gap in knowledge transfer from early formulation development to commercial, there is seamless progression into late stage development.

Case study

Clinical Assessment of Maralixibat for Rare Pediatric Liver Disease via Real Time Personalized GMP Manufacturing

Maralixibat is being developed for the treatment of rare pediatric liver diseases, Alagille Syndrome, an autosomal genetic disease, and Progressive Familial Intrahepatic Cholestasis, a group of cholestatic conditions. A high level of customization of the drug product was required to support an extensive Phase II/III clinical program based upon mg/kg dosing of patients, and the potential need to adapt the product during the treatment phase if there was a change in body weight of >10%. A real-time adaptive

platform was configured which enabled a bespoke, personalized solution product to be manufactured, labelled and supplied on a global basis ready for dosing within 1-3 weeks of subject eligibility being confirmed⁸. Products were re-supplied to each patient every 1-3 months based on individual needs and response to treatment. In total 6 studies were supported involving the manufacture of over 2000 individual products for dosing in over 180 patients across 27 sites in 9 countries.

Commercial manufacturing

The manufacturing challenges faced in the late-stage development and commercialization of orphan drugs for rare diseases can be significant, requiring a triangulation and management of low volume demands, small batch sizes, limited API availability and high variability in product configurations. Quotient has significant experience in using our diverse and flexible capabilities across multiple manufacturing platforms to work with our customers to configure a robust manufacturing and supply chain to meet these requirements for both adult and pediatric dosage forms. We continue to invest in small scale commercial equipment to broaden the technologies and product formats available and ensure seamless continuity throughout the development life-cycle. We are passionate that this differentiation is in keeping with market trends given fewer products in the future will have traditional “blockbuster” potential in terms of volume and sales. Conventional manufacturing approaches to commercialization will no longer apply.

Quotient also excels in the handling of high potency APIs which can provide challenges to other contract manufacturing partners. We have multiple potent and non-potent suites with containment options which allow us to produce drug products with APIs with operator exposure limits (OELs) of $<1\mu\text{g}/\text{m}^3$ (equivalent to PBLEC level 5 / Safebridge category 4). We also have DEA capabilities for the handling of scheduled substances.

In addition to our manufacturing capabilities, Quotient utilizes a robust supply chain to provide value to our development and commercialization partners. We maintain sufficient QA/QC released stock of general use excipients used in both tableting and encapsulated



production to reduce production start-up time to avoid waiting to receive and release raw materials. An established global supply chain with raw material manufacturers, vendors and suppliers in both the US and EU allows Quotient to reduce procurement downtime, especially when combined with our network of internal and external release testing laboratories which increases flexibility to minimize raw material release times. Quotient maintains multiple approved vendors for shipments to allow rapid turnaround to packagers and clinical sites.

Quotient Sciences is a global player in commercial manufacturing of small molecule products including niche therapies such as oncology, orphan and pediatric indications. The experience we have from multiple successful launches allows us to accelerate development programs through registration and process validation. Our manufacturing facilities support manufacturing batch sizes ranging from less than 1 kg to 500 kg for solid oral dosage forms and up to 350 L for liquid formats. Whether you are preparing for ANDA, NDA, MAA or Japanese NDA, Quotient has the expertise and regulatory approval to manufacture your registration and validation batches for the U.S., U.K., Europe and Japan. The Quotient team also has significant experience of supporting 505(b)(2) and all post-approval change filings.

The Quotient Solution

The development of new therapeutics to treat rare disease continues to attract increasing industry activity. Whilst formulation and drug delivery requirements are comparable with those across all therapeutic areas, unique challenges are presented to development companies. Market potential will mean an even greater focus on managing program time, cost and risk. Lean and flexible programs will be imperative to progress molecules effectively and efficiently from candidate selection through to commercialization. By definition, access to patient populations during clinical research will be challenging and may require increasing personalization of the drug product based on individual patient needs. A flexible manufacturing and supply

platform will be key. Finding the right commercial manufacturing partner will be challenging given the relatively low production volumes required and the high variability in product formats and configurations.

At Quotient Sciences we have supported over 50 development programs for rare disease in the past 5 years. Our extensive formulation know-how coupled with our agile and flexible approach to clinical and commercial manufacturing, makes us the ideal partner to provide an end-to-end solution for the development of orphan drug products.



References

1. US Orphan Drug Act (1983)
2. EU Orphan Drug Regulation EC141/2000
3. www.rarediseaseday.org/article/what-is-a-rare-disease
4. J.M Butler and J.B. Dressman (2010) The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development. *J. Pharm. Sci.* 99(12), 4940-4954.
5. EMA Reflection Paper: Formulations of choice for the paediatric population (2006)
6. EMA Guideline on pharmaceutical development of medicines for paediatric use (2014)
7. DiMasi, J and Wilkinson, M; The Financial Benefits of Faster Development Times: Integrated Formulation Development, Real Time Manufacturing, and Clinical Testing. TIRS. Published June 2020.
8. N. Whitfield, N. McEntee, E. McGriskin, C. Upton, A. Church and P.D. Scholes (2017). Enabling Clinical Assessment of Maralixibat for Rare Pediatric Liver Disease via Real Time Adaptive GMP Manufacturing. AAPS Conference, Poster W1042

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