



# Accelerating the Development of Oncology Medicines



## Introduction

**Oncology drugs dominate today's research focus with over >5500 molecules in development, representing over 35% of the total industry pipeline<sup>1</sup>. 10 new oncology drugs were approved by FDA in 2019, of which half had an orphan indication and all had been granted priority review<sup>2</sup>.**

Given the number of molecules in development, there is increasing pressure on development teams to identify successful drug candidates as quickly as possible, and accelerate patient access, particularly where no effective therapies are currently available. However, the oncology therapeutic area remains a challenging one to navigate and success rates are low. The likelihood that a molecule entering Phase I will reach market is around 10%, with the average duration of an oncology clinical trial taking 40% more time than other therapy areas.

Oncology drug development has seen a significant shift in focus over the past 20 years as molecule chemistries and drug technologies have improved. Historically most oncology drugs were cytotoxic compounds with poor safety profiles. However, in recent years a better understanding of cancer aetiology has improved drug target specificity of oncology compounds, leading to the advent of molecular target agents (MTA), with more favorable safety profiles. Targeted small molecules currently make up around 40% of the global oncology pipeline, whereas cytotoxins have fallen to just 7%<sup>3</sup>. This movement has opened the opportunity to use more convenient dosage forms, with oral administration considered the gold standard for patient compliance. Understandably, compared to the intravenous dosage form, this move to oral administration brings a different set of biopharmaceuticals challenges that need to be overcome.

As a fully integrated drug development and manufacturing organization, Quotient Sciences is well positioned to address the challenges associated with developing small molecule oncology therapeutics, supporting biotech and pharmaceutical companies in accelerating drug development timelines from candidate selection through to commercial manufacture and supply.

This white paper will discuss five areas for consideration by oncology drug developers and the potential solutions which are emerging:

- > Formulation development
- > Clinical development: accelerating to POC
- > Formulation optimization and validation of product performance in humans
- > Process development, "scale-up" & clinical manufacturing for Phase II/III
- > Commercial manufacturing & supply

### Quotient's Oncology Experience 2015 – 2020

**342 projects**

On **91** different molecules

With **66** clients

Spanning **34** disease indications

## Formulation development

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 oncology 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, typically in a patient population, with a fit-for-purpose formulation which maximizes the potential for clinical success? How can we minimize the impact of formulation changes during development?

To maximise the probability of success of any drug product development program the physicochemical properties of the molecule need to be considered at the earliest stages of development and optimized through iterative rounds of medicinal chemistry to design out sub-optimal properties where possible. Supportive preformulation work evaluating solubility of different salts, co-crystals and polymorphic forms and preliminary evaluation of compound permeability and stability is invaluable in guiding candidate selection. Upon candidate selection preclinical formulations can be developed to maximize drug exposure and provide sufficient toxicological cover to support clinical development.

At Quotient our pharmaceutical scientists use the Developability Classification System (DCS)<sup>4</sup> as a powerful tool to identify drug delivery challenges based on the solubility and permeability of the compound, and from that define the formulation development strategy. The clinical performance of DCS class I molecules – with good solubility and permeability – can be rapidly evaluated with confidence in Phase I patient studies using simple, fit for purpose product formats such as drug-in-bottle, or more typically solid dosage forms including capsules or simple immediate release (IR) tablets. These provide for the greatest amount of dose flexibility needed in the early stages of development and allows the phasing of CMC investment until initial efficacy data are confirmed and key program milestones met.

The vast majority of NCEs however present challenges to their bioavailability – in terms of their solubility and/or permeability – resulting in low and variable pharmacokinetics, sub-optimal or non-proportional exposure and/or positive food effects. In this case a wide range of formulation tools are available varying in complexity and their appropriateness depending on the DCS class. DCS class IIa molecules are poorly soluble due to their dissolution rate, so strategies such as micronization or nanomilling may be effective. DCS class IIb molecules are solubility limited and may require development of an amorphous dispersion or lipid formulations for example.

Quotient's approach prioritizes 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 based on the DCS system. With biopharmaceutics experience and knowledge, we 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.



## 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 in downstream development? Key to success we believe will be the drug product, but first there is a more strategic development consideration: Will the molecule begin clinical evaluation in patients or healthy subjects?

### The First-in-Human Trial: Patients or Healthy Subjects?

With an increasing number of targeted therapeutics in the oncology pipeline there has been a paradigm shift in Phase I clinical testing. Whereas before sponsors had no choice but to conduct their FIH clinical studies in patients, molecules with much improved safety profiles have created the possibility of early phase testing in healthy volunteers which brings a number of benefits:

- > Less variability within the population
  - > More consistent physiology, and absence of comorbidities makes analyzing pharmacokinetic and safety data cleaner
- > Logistically less challenging
  - > Healthy volunteer oncology study can be conducted at a single site, using a ubiquitous population
- > Performance of the drug product can be determined and optimized if necessary, prior to entering patient studies, reducing development risk
  - > Solubility enhancing technologies can be evaluated and selected to ensure optimum performance
  - > Modified release (MR) formulations can be developed if the compound exhibits sub-optimal pharmacokinetics, to reduce adverse events or frequency of dosing

When dosing an oncology molecule in healthy volunteers, it is important to consider differences in regulatory expectations between patient and healthy volunteer studies. For example, the nonclinical package requirements for dosing healthy volunteers is more extensive than for patients, so some additional nonclinical studies will be required (Table 1).

**Table 1:** Types of nonclinical studies required for first in human studies in healthy volunteers versus patients, assuming a once every 2 to 3 week dosing schedule for the first in human

Study type	Data provided	Healthy volunteer	Patient
Safety pharmacology	Mechanism of action	X	X
	Vital organ function	X	X
Pharmacokinetics	AUC, C <sub>max</sub> , T <sub>1/2</sub>	X	X
	Metabolic and plasma protein binding	X	
Toxicology	NOAEL	X	
	Recoverability	X	X
	2-week repeated dose study	X	
	Single dose study	X	X <sup>a</sup>
	Male fertility (as part of general tox study)	X	X
	Photosafety (as required)	X	X
	Combination drug product tox (as required)	X	X
Genotox	Assay for gene mutation	X	
	Chromosome damage in mammalian systems	X	

Another key consideration is ensuring study objectives are appropriate to their study population. Reaching maximum tolerated dose is a common objective in FIH oncology patient studies, however dosing to intentionally observe an adverse event in healthy volunteers is considered unethical, and is likely to be considered as grounds for non-approval from regulators.

Of course, one of the major downsides to the use of healthy volunteers instead of patients is the lack of efficacy data. An initial proof of pharmacological effect arm in a study can provide invaluable reassurance to a sponsor prior to starting Phase II patient trials. For certain molecules however it may still be possible to generate data in healthy volunteers with clinically relevant biomarkers as surrogate markers for efficacy (see Case Study 1).

### Case study 1

## MEI Pharma: Formulation flexibility in the FIH trial to accelerate to POC

A first in human study was conducted in healthy volunteers to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of oral ME-401 a Pi3K  $\delta/\eta$  inhibitor. This FIH study used a leapfrog SAD design as an efficient use of subjects, and assessed inhibition of basophil activation to demonstrate proof of pharmacological effect (PoPE). The option to screen different formulation technologies was built-in to the protocol, in case sub-optimal clinical PK data were observed. A combination of real-time manufacturing of drug products and a flexible clinical protocol, allowed the emerging clinical data to inform decisions on the formulation compositions, allowing adjustments both to dose escalate and ensure desired systemic exposure. Small batch manufacturing helped to conserve drug substance and significantly shorten the timeline to starting POC with a patient-friendly oral dosage form<sup>5</sup>.



Figure 1: Case study 1 overview



## Flexible Clinical Manufacturing and Supply for Patient Trials

The development norm for oncology however remains a progression direct to patients, to understand efficacious potential in a population often without other treatment options. It is recognized that oncology 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. There may also be a need for personalization of the drug product linked to patient attributes such as body weight / surface area or genetic markers. As such, the supply chain for oncology programs can be complicated based on numbers and types of patients to be enrolled in the clinical trial, number of countries participating, the regulatory requirements of those countries as well as individual patient needs. Quotient has been providing supply chain solutions for oncology projects for over a decade and is perfectly positioned to support complex clinical trials of this type.

Traditional large batch manufacturing of tens of thousands of dose units and multiple strengths has its place in the industry. However, increasingly these conventional drug product supply chains are not properly geared for oncology trials, with molecules that may be designated orphan or rare disease status. These may require small batch sizes, low volume requirement

per year and product customization. A flexible model is therefore 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 personalized manufacturing. Table 2 compares and contrasts the benefits of traditional batch manufacturing with personalized manufacturing. 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

## Formulation optimization and validation of product performance in humans

Given the biopharmaceutical challenges of today's molecules, it is not uncommon to observe a gap between observed and desired performance following initial human trials, necessitating an optimization of the drug product. How best can these deficiencies be addressed? At Quotient Sciences we have demonstrated that formulation flexibility in healthy volunteer trials can be used to develop "patient ready" formulations for oncology molecules in less than half the time of the industry standard<sup>6</sup>. This is accomplished by the close integration of real-time manufacturing and clinical testing, or Translational Pharmaceutics, which uses a 14 day "make-test" cycle, enabling formulation decisions to be made on the basis of emerging human data. In Case Study 2 the relative bioavailability of three novel hydrobromide (HBr) salt formulations were assessed in comparison to the reference free base formulation.

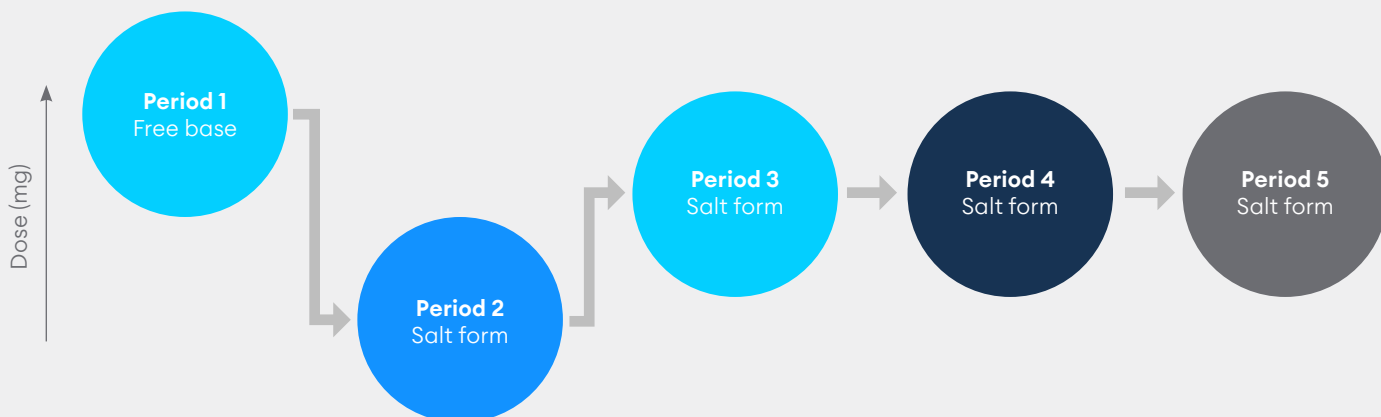
### Case study 2

## Clovis Oncology: Formulation optimization in healthy volunteers

A five-period sequential study was performed to assess the relative bioavailability of 3 novel hydrobromide (HBr) salt formulations of oral CO-1686, an epidermal growth factor (EGF) inhibitor, versus a reference freebase (FB) formulation. Phase I studies had identified that the FB form exhibited non-linear systemic exposure and variable PK. A HBr salt form was identified to improve exposure. An integrated program design allowed real-time adjustment of

tablet dose strength in response to emerging clinical data prior to subsequent dosing periods. Additional alternative tablet excipients were also evaluated in periods 3, 4 and 5 to further optimize bioavailability. The use of healthy volunteers is allowed for rapid formulation assessment and screening, and identified a successful HBr salt formulation which exhibited a 2-fold increase in relative bioavailability compared to the original free base formulation<sup>7</sup>.

Figure 2: Case study 2 overview



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

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. 50-500 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. This is particularly relevant for oncology drugs where many will be on accelerated development pathways with regulators.

Quotient applies the principles of Quality by Design (QbD) in early 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 define 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 biopharmaceuticals 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.

### High Potency Handling

Global demand and growth in targeted oncology therapeutics has led to an increase in the manufacturing of high potent active pharmaceutical ingredients (HPAPIs). This has driven the need for high potency handling capabilities, particularly high-containment manufacturing facilities. Handling of these ingredients in the drug supply chain requires specialist equipment to be employed to avoid cross contamination, product protection and to ensure operator and environmental safety.

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.

### Registration Batches and Process Validation

As a product moves into the later stages of development for Phase III trials, registration phase preparations begin for a successful commercial launch and supply of the product. The flow chart below shows a high-level overview of the various processes from registration batch production to commercialization.

How Quotient can help you efficiently scale-up the drug product manufacturing processes





## Commercial manufacturing & supply

The manufacturing challenges faced in the late-stage development and commercialization of oncology drugs 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.

Quotient Sciences is a global player in commercial manufacturing of small molecule drugs for 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 batch sizes ranging from less than 1 kg to over 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 CBE-30 filings and all post-approval change filings.

Currently, Quotient manufactures two first-in-class oncology products for global pharmaceutical companies. One product is the first and only once-daily PARP inhibitor for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The second product is the first therapy specifically for patients with advanced RET-driven lung and thyroid cancers. In both cases, Quotient supported the early stage product, through registration, process validation and successful commercialization.

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.



## 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.

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## Who is Quotient Sciences?

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, molecules need to become cures, fast. Because humanity needs solutions, fast.

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