Quotient Sciences

Molecule to cure. Fast.™

Information sheet

Accelerating development of 505(b)(2) products

- Are you developing a new dosage form for an existing drug?
- Do you need to explore a different route of administration?

Why is Quotient a good partner for the development of 505(b)(2) products?

Quotient has significant experience in 505(b)(2) product development and can support you in efficiently turning your innovative ideas into successful products. Over the past several years, the FDA's 505(b)(2) regulatory pathway has enabled the approval of a variety of differentiated dosage forms for existing molecules[1, 2]. There has been an increasing number of product approvals in the US using this approach and similarly, in the EU, the Hybrid Medicine Authorization process can provide new product opportunities for previously approved compounds.

At Quotient, we have the expertise to develop, characterize, manufacture, test and support products intended for major routes of delivery with extensive experience in solid oral dosage forms. Quotient has the experience and flexibility to work with drug delivery technology platforms to overcome solubility limitations and to produce drug products with improved bioavailability that can lead to lower doses, reduced variability and elimination of food effects.

Dosage form development and manufacturing expertise

With state-of-the-art facilities in the UK and US and a global team of formulation and analytical experts, Quotient provides a data-driven approach to formulation development to achieve your target product performance. We prioritize the key API characterization data required and develop formulation strategies 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 technologies and novel drug delivery systems.

We also recognize that many drug delivery technology companies will also seek to leverage their formulation know-how to repurpose existing drugs via the 505(b)(2) pathway. Quotient has significant experience in the technology transfer of products, processes and equipment into our GMP facilities to be your manufacturing partner. Uniquely we can also adopt "formulation design space" concepts where possible in the development of your products, to quickly identify the optimum formulation compositions that meet specific clinical performance criteria.

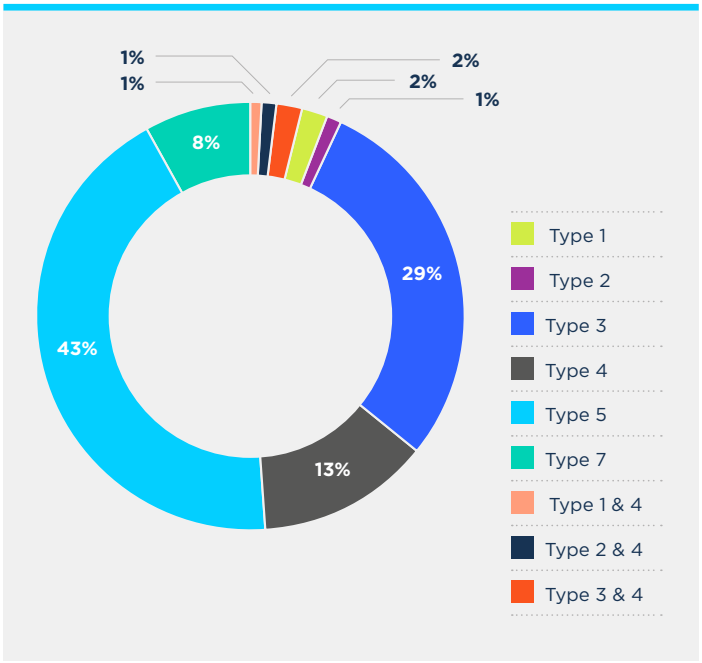
Our experience covers various regulatory submission classification types[3] shown in Table 1. The most common categories used in the development of 505(b)(2) products are shown in Figure 1. Quotient's formulation development group can be used as an extension of your team to explore diverse formulation strategies and lock various intellectual property rights that protect the product life cycle. With flexibility and experience in working with non-proprietary and proprietary drug delivery systems, we support clients that require specific processes and equipment for manufacturing cGMP batches for clinical trials and commercial markets. Quotient has provided solutions to enable the use of conventional technologies for early dosage form development and made them successful by progressing them from clinical manufacturing through commercial development.

Table 1: FDA Submission Classification Types for Product Approval

Classification type	Definition
1	New molecular entity
2	New active ingredient
3	New dosage form (could include a changed formulation, a new route of administration, an altered excipient, or a new strength).
4	New combination
5	New formulation or manufacturer
6	New indication
7	Drug already marketed without an approved NDA
8	OTC switch
10	New indication submitted as a distinct NDA

OTC = over the counter NDA = New Drug Application

Figure 1: Comparison of classification types used for 505(b)(2) products over a five year period



Integrated clinical pharmacology & data sciences

At Quotient, we understand the importance of quickly generating the critical clinical data necessary for supporting a 505(b)(2) application. Quotient has a dedicated team of pharmaceutical and manufacturing scientists, clinical pharmacology and biopharmaceutics experts, medics, project managers, data science experts, medical writers and regulatory personnel within our organization. At Quotient's in-house clinical pharmacology units in Nottingham, UK and Miami, US, we tailor the design, conduct and reporting of the key clinical studies relevant to 505(b)(2) development including relative bioavailability, food effects and pivotal bioequivalence (BE) assessments with either pharmacokinetic (PK) and/or pharmacodynamics (PD) endpoints. Studies can be performed to assess a full spectrum of new formulation technologies, Immediate Release (IR) to Modified Release (MR) switches, alternative routes of delivery, a comparison of multiple Reference Listed Drugs (RLDs) and the new combination products, to name a few.

Quotient's Data Sciences experts provide bespoke services for early phase clinical studies including data management, eCRF programming, statistics and statistical programming, pharmacokinetic modelling and simulation, and medical writing. These capabilities deliver real-time data to customers for review and interpretation, enabling crucial product development decisions to be made during a study including changes to formulation composition or dose level.

Accelerated clinical evaluation and product development using Translational Pharmaceutics®

Quotient's unique Translational Pharmaceutics® accelerates drug development by integrating formulation development, real-time manufacturing and clinical testing. The platform is unique to Quotient Sciences and has been used over the last decade by global pharmaceutical and biotech companies across more than 400 drug programs.

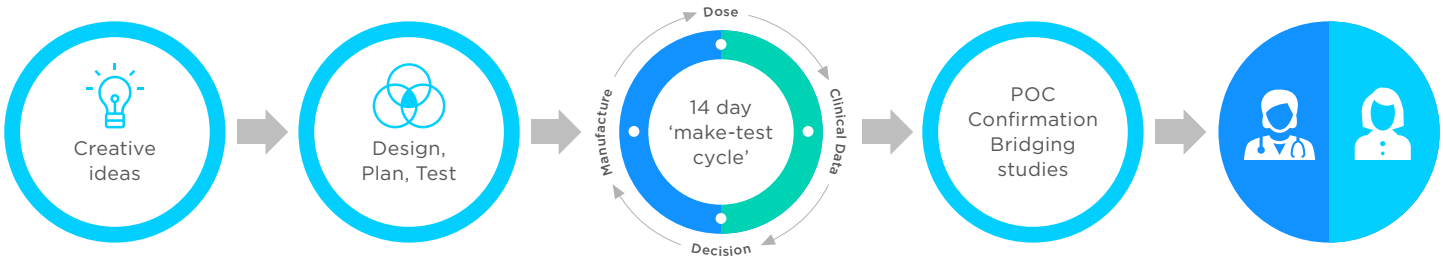
A recent publication[4] by Tufts CSDD shows that biotech/pharma companies save on average >12 months of development time compared to traditional development models. This translates into R&D cost savings of >$100 million as well as the benefit of getting products to market much sooner.

Unlike traditional drug development, Translational Pharmaceutics integrates a wide array of activities under a single service provider. This reduces the "white space" in development and shortens times between clinical manufacturing and dosing, from months to days. Simple or complex drug products are manufactured in real-time during the clinical study, with arising human data used to inform the composition of the next formulation to be manufactured and dosed. Formulation compositions can therefore be modified using rapid "make and test cycles" working within formulation design spaces to develop and optimize a variety of dosage forms. Programs are led by a highly skilled cross-functional project manager and science team offering data-driven decision-making.

Translational Pharmaceutics® is therefore an ideal platform to support 505(b)(2) programs, where there is often uncertainty on formulation compositions to achieve clearly defined product performance and PK criteria.

Clinical data can be used to "tune" the performance in pilot or exploratory relative bioavailability studies prior to committing to pivotal regulatory BE study with increased confidence on the probability of success.

Accelerated clinical evaluation and product development programs



Quotient has the knowledge and experience to efficiently scale your process to meet the requirements of pivotal registration studies

After identifying a lead formulation, the optimized drug product will be scaled up and progress into a pivotal regulatory BE study, in either volunteers or patients, with either PK, PD or therapeutic endpoints. Quotient provides the full capability for clinical manufacturing, packaging, labelling and supply, maintaining multiple approved vendors for shipments that enable rapid turnaround to packagers and clinical sites so your studies can run smoothly.

Quotient will help you efficiently scale-up drug product manufacturing processes to meet the demands of your pivotal registration studies and ensure seamless transition to larger scale manufacturing and 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, with equipment trains for scaling up pharmaceutical manufacturing processes from gram quantities to multi-kilogram batches (e.g. 500 kg) for tablets and capsules.

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 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.

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

Readiness for Commercial Manufacturing

Quotient's capabilities encompass all your production needs with diverse experience across multiple manufacturing platforms. Quotient can perform technology transfer, scale up, process validation and commercial manufacturing of your 505(b)(2) product. Quotient tracks and trends all batches manufactured from process validation to commercial batches manufactured as part of its internal Continuous Process Verification (CPV) program and therefore supports a product robustness capability rarely seen in CDMOs.

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 Sciences is a global player in commercial manufacturing of small molecule products spanning all therapeutic areas and 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 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. Quotient has the expertise and regulatory approval to manufacture your registration and validation batches for the U.S., U.K., Europe, Brazil and Japan. The Quotient team also has significant experience supporting 505(b)(2) and all filing types in a timely manner couple with the knowledge, experience and the flexibility to supply the markets of intent.

Other key services to support your 505(b)(2) product development

- **Pre-formulation and material science:** Quotient has expertise in physico-chemical testing of API, salt and polymorph screening and solid state characterization
- **Scintigraphic imaging:** Quotient has 30 years' experience in this technique to visualise the transit of dosage forms through the GI tract and provide valuable information for the design and optimization of dosage forms (e.g. modified release systems).
- **Modelling and simulation:** At Quotient we can use preclinical and clinical data to guide formulation development and optimization as well as inform pediatric dosage form development. A robust M&S strategy can also be used to support changes in dosing regimens[5] in 505 (b)(2) applications in place of or in addition to clinical testing.
- **High potency handling and controlled substances:** Quotient has the state-of-the-art containment manufacturing for handling high-potency products with operator exposure limits (OELs) of <1 $\mu g/m^3$ (equivalent to PBLEC level 5 / Safebridge category 4). We also have DEA capabilities for the handling of scheduled and controlled substances.

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