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A Road Map To Expedited Review Pathways

For many years, accelerated development and manufacturing timelines have provided developers with paths to move new therapies to market quickly while still maintaining a balance of risk/benefit assessment for patients. Regulatory agencies around the world, including the U.S. FDA, EU EMA, Health Canada, Japan PMDA, Chinese NMPA, and Brazilian ANVISA, offer expedited approval pathways that are applicable when new products are filling unmet medical needs for certain targeted diseases or conditions.

In the U.S., key differentiators between the Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval designations include the program requirements and their allowances in terms of agency guidance, review process, approval time and/or use of surrogate clinical endpoints for supporting clinical benefit. These designations can occasionally be stacked, with programs often having multiple designations. In fact, the CDER report "Advancing Health Through Innovation: New Drug Therapy Approvals 2024" states that 75% of novel drugs the FDA approved in 2024 used one or more of these designations.

Drug developers should ask themselves several questions to determine the applicability of one or more accelerated pathways to their product:

- Would the drug treat a life-threatening indication?
- Would the drug fulfill an unmet need?
- Are there significant improvements over current standards?
- What is the patient population worldwide?
- When does the disease onset, and at what age are patients diagnosed?

Therapies for rare and orphan disease are the most likely to utilize one or more accelerated pathway designations, but unmet needs in areas including oncology can also typically receive these designations. Understanding the timing of disease onset and diagnosis is a crucial, but often overlooked, facet of the equation. The answer informs which different dose forms and formulations may need to be developed, particularly when the disease impacts pediatric or geriatric patient populations.

The cumulative answers to the above, how they shape the risk/reward for the patient, and the clinical significance of perceived benefits are the basis for early conversations with regulators. Since other global health agencies' expedited approval programs feature functionality and incentivization similar to the FDA programs, the fact-finding and operating principles described here are applicable to many of those processes, as well.

For example, the EU EMA offers an accelerated assessment process and PRIME designations. Following BREXIT, the UK's MHRA introduced the Innovative Licensing and Access Pathway (ILAP). Japan's PMDA also offers priority review timings and Sakigake designations for breakthrough therapies.

Success and Failure are Collaborative

When a sponsor partners with a CDMO, it should seek a partner with experience and knowledge in the challenges often encountered during development. For example, the patient population for a rare disease treatment will be, by definition, smaller than patient populations of more widespread diseases. Governments recognize this and incentivize research by providing added value, such as grants or exclusivity on patent protection. However, finding vendors willing to make as little as one commercial batch a year at a relatively small volume, while still ensuring high quality, can be difficult.

Pursuing an expedited approval pathway requires choosing a CDMO that embraces shared ownership for success in the product and strives to understand the sponsor's goals. In cases where a sponsor has not developed and/or commercialized a product before, the sponsor is not only navigating expedited approval with little background in technical, regulatory, or operational areas, but they may also be looking for licensing and divestment strategies (i.e., seeking a trusted partner or attempting to sell the asset). In these situations, an adept CDMO partner can help the sponsor establish a development road map early and preserve continuity in anticipation of the asset potentially being transferred to another partner later.

Proactive team collaboration enables faster, more calculated actions when rapid changes in development become necessary. The CDMO must be able to create a tailored target product profile (TPP) and control strategy, since each product will have unique development gaps and patient-specific needs, as well as be flexible enough to execute strategy changes throughout the accelerated timeline.

Additionally, a sponsor and its CDMO partner must consider available resources to meet the risk associated with compressed timelines. Access to internal technical expertise and other required resources will differ between organizations based on their size, funding sources, partnership models (e.g., academic/private), and more, as will their financial targets and funding milestones. Resources must be balanced accordingly to achieve product needs specific to the program's phase of development. Aligning resources and asset inflection points while de-risking the product's early development milestones is an important, ongoing conversation throughout the partnership.

For example, Quotient Sciences, an industry specialist in addressing clinical needs in rare disease treatment, can make small, just-in-time batches to support clinical studies for a product with API restrictions such as high cost, limited availability, or long production times, in addition to patient specific dosing regimens or recruitment. Early in a clinical program, navigating API challenges in conjunction with flexible dosing requirements can be difficult for sponsors.

Turnover of subject matter experts throughout a program is another challenge exacerbated by tight timelines. Utilizing consultants to help fill gaps and support various aspects of a program is an approach taken by many developers but may only be a temporary solution. An individual brought on for a project-based engagement, for example, may be committed to another company or project by a certain date, limiting the sponsor's ability to extend collaboration with that consultant. Working with a knowledgeable partner like Quotient Sciences means consistent and dependable support from an experienced professional team that can follow the molecule for the entirety of the program.

Development and Delivery are Survival Skills

Facing potentially accelerated approval pathways, regardless of location, drug sponsors and their partners must quickly identify formulations suitable for first-in-human (FIH) clinical trials, typically with limited API available for development and/or clinical trials. As development moves rapidly through proof of concept, the demand for having a robust, scalable, commercial-ready drug product approaches faster than generally anticipated. Failing to properly characterize and understand the API's properties early on may advance the wrong dose form into FIH studies.

As a result, researchers may incorrectly conclude a product is ineffective or poorly designed, and they may abandon a viable molecule because they used a sub-optimal product format. Taking an integrated approach that combines development, manufacturing, and flexible clinical dosing enables concurrent development and screening of multiple formulations in FIH studies. This allows developers to maximize clinical options by producing small, cost-effective batches for rapid iteration of dose forms and efficient assessment of the product's druggability. In silico predictive tools, such as modeling & simulation, assist in this effort.

Once a suitable dose form is identified, it must be examined for viable scale-up strategies and clinical trial material delivery pathways. Due to the considerable time it takes to manufacture, package, label, and ship to clinical distribution hubs, a long shelf life also is crucial in traditional batch manufacturing. Additionally, much of the manufactured material is used to support stability testing instead of treating patients in clinics.

As such, the cost of goods or cost of production can be determining factors between dose forms. Flexibility in the products taken to the clinic, without a significant investment in large batches, is crucial to balancing a budget while de-risking the program as much as possible. Developers can work with their partners to find creative solutions to overcome these hurdles.

For example, Quotient Sciences leverages the synergy between its in-house development and manufacturing teams to accelerate early-phase study supplies, requiring only days of stability data instead of the typical months or years. Speed is of the essence when quickly manufacturing drug product to supply FIH trials that generate pharmacokinetic (PK), tolerability, and safety data. Without an integrated approach and calculated distribution logistics, this can be an exceedingly wasteful and time-consuming process.

Just-in-time production, closely coordinated with product development, is another important factor in the clinical trial materials supply chain. Common questions at the start of a program generally focus on the API requirements (how much API is available and when is it available?), but more specifically, GMP-quality API that can be turned into a clinical product may have a different timeline to produce. Knowing the answers to these questions as early as possible helps both the sponsor and the CDMO proactively identify supply chain risks and develop strategies for future technology transfer, manufacturing, and distribution.

Figure 1: Tailored clinical manufacturing provides flexibility

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

Do More With Less

"Do more with less" does not just refer to API usage during formulation development. The phrase also speaks to the need to speed through expedited approval pathways while obtaining meaningful development data and maintaining product quality, despite the compressed timeline. This is where the quality of scientific support and supporting teams is critical.

At Quotient Sciences, drug development consultants (DDCs) are at the center of this effort, amassing industry and technical knowledge into a strategic overview of the drug program that keeps the client's goals in mind. DDCs assist customers in designing the clinical program, clarifying key decision points (along with any of their pros/cons and repercussions), and ultimately helping to reach key development milestones.

Moreover, for integrated development activities to be successful, project management must be thoroughly involved in a drug program. Project managers assist with sponsor accessibility to departments and services provided by the CDMO partner, enabling clients to ask questions, exchange ideas between various teams, and discuss development – from early stages through to commercialization processes, as necessary. All parties should understand and agree on the plan so, when things change, they understand the contingencies in place.

In many companies, the teams that develop the drugs are siloed from clinical personnel. Sometimes, the first time those groups engage with each other is when they work with a CDMO that facilitates those interactions. By contrast, the skills and mindset required to work at the expedited approval pathway tempo is ingrained into how Quotient Sciences operates – from project management through to the distribution teams. This experience helps customers to maintain control of their programs and instills confidence in their up-to-the-moment understanding of key program elements.

Expedited approval pathways require late-stage development overlap with ongoing clinical, CMC, and regulatory work. Stability and process data may rely on concurrent validation approaches with conditionally approved commercial launch. The drug's approval may be contingent on data that continues to be generated while clinical studies and the production process are ongoing, with potential gaps still existing. Therefore, those gaps must be identified, characterized and de-risked to ensure that a product approved using one of these pathways does not present a risk to patients while awaiting clinical endpoint data and full marketing authorization.

Quotient Sciences helps customers navigate the development pathway, meeting the regulatory requirements of a product granted expedited development and review, as well as generating data needed to support drug approval. It is important to remember that the agency recognizes the complexities associated with expedited approval timelines and is eager to work with drug developers that are motivated to bring these products to market.

Regulatory Collaboration Continues to Expand

Moving forward, the industry can likely expect to see additional expedited approval pathways to cover more therapeutic areas and continued commitment by regulators to open conversation at all stages of development. To provide additional support, the FDA launched the Chemistry, Manufacturing, and Controls Development and Readiness Pilot program in April 2023 to help companies navigate and prioritize their CMC resources commensurate with their development pathway.

Still, the critical issue in developing products via expedited approval pathways is not the presence of inherent risks. Rather, it is the failure to adequately prepare for and mitigate those risks. An experienced CDMO will help its partner prepare for common requests and inquiries during this process. At Quotient Sciences, this support includes helping sponsors anticipate questions and proactively formulate responses for regulators (along with presenting the necessary evidence and documentation to back up answers), plan regulatory submissions and a pre-approval inspection (PAI), and facilitate mock inspections between quality, regulatory and CMC teams.

As new technologies, unpredictable geopolitical occurrences, and increasing demand for services add to the burdens of drug development and manufacture, it is imperative that sponsors maximize operational efficiency and minimize associated risk. A key way to accomplish this is by taking advantage of the expedited approval pathways offered by regulators around the world, and an experienced CDMO partner can light the path.

About the Experts

Brad Rowe, Senior Director, Integrated Development
Quotient Sciences

Brad Rowe, based in Philadelphia, PA, joined the organization in 2005. In his current role, Brad helps the Quotient Sciences business unit teams discuss and scope programs with clients, supporting program operations as a technical advisor throughout the lifecycle of a program.

Robert Cornog, Senior Director, Product Development
Quotient Sciences

Robert Cornog has over 26 years of experience in product development and process design. In his current role, Robert provides technical and scientific support for the successful transfer of late-stage and commercial drug product programs at Quotient Sciences.

About Quotient Sciences

Quotient Sciences provides integrated services for advancing small molecules and synthetic peptides along accelerated approval pathways. We provide integrated contract research, development, and manufacturing (CRDMO) services to leading Fortune 100 global pharma companies as well as emerging biotech organizations, bringing deep expertise and trusted insight to every program. To learn more, visit **www.quotientsciences.com**.

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