Know Your Product, Know Your Path: A Primer on Advanced Therapy Development

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Translating an R&D asset into a human therapeutic is a risk-filled endeavor that can be further complicated by a wide range of potential manufacturing challenges during development. For this reason, biomanufacturers must have a comprehensive understanding of their process and product. This knowledge will enable them to optimize manufacturing processes, efficiently troubleshoot any issues, and ensure regulatory compliance.

However, small biopharma and academia — often credited with being the primary drivers of innovation[1] — sometimes struggle to make the shift from a research mindset to a commercial one. This is due to several reasons but, most notably, these originators typically lack the specialized expertise and resources necessary for developing robust manufacturing processes. Immature manufacturing processes can result in variable product quality and, eventually, to delays in regulatory approval. To prevent setbacks that can slow the path to market, it is critical to develop a CMC strategy that proactively identifies scientific and compliance gaps and mitigates risk.

First, Adopt a Quality by Design Mindset

While Quality by Design (QbD) could be defined as simply a rigorous set of predefined experiments and actions, it is much more. More accurately, QbD is a development framework that integrates product and process knowledge throughout the commercialization life cycle, emphasizing quality and risk mitigation from the very beginning. Through a deeper understanding of a product's critical quality attributes (CQAs) and the critical process parameters (CPPs) that influence them, manufacturers can prevent knowledge gaps and design a process and control strategy that ensures a product will consistently meet today's rigorous quality standards.

Unfortunately, many sponsors do not thoroughly define their product. They have not developed an unambiguous target product profile (TPP), which describes the drug product's intended use, or a robust quality target product profile (QTPP), which identifies the drug product's critical quality attributes. For emerging products like cell and gene therapies, applying QbD during development helps maintain precise control over consistency and quality, despite the unique nature of these products. Proceeding with process development (PD) without these integral components of the QbD framework increases the risk of regulatory challenges, clinical holds, and other program delays.

A QbD mindset also helps prioritize activities, which can ensure efficiency in the face of constrained resources. For example, consider a project that has limited time/resources to conduct the full range of testing often needed early in development. QbD tools can help the sponsor and, if applicable, its outsourcing partner, to identify and pursue high value-added activities.

Interweave Regulatory and CMC Strategies for Maximum Benefit

When developing advanced therapies, it is vital to marry regulatory and CMC strategies because complex biological products develop quickly in the clinic. So, if these strategies are not developed early and in alignment with one another, the sponsor potentially risks discovering that significant process changes are necessary in the midst of a pivotal clinical trial.

Fig. 1 depicts a general overview of CMC needs and actions from development through postmarket monitoring. By designing CMC and regulatory strategies essentially in parallel, sponsors acknowledge and embrace the need for manufacturing development to correspond with clinical-phase development. Sponsors often have a good idea what might be necessary from a clinical standpoint, but they do not flesh out as fully — from a manufacturing standpoint — which types of data will be necessary or which types of studies will produce those data.

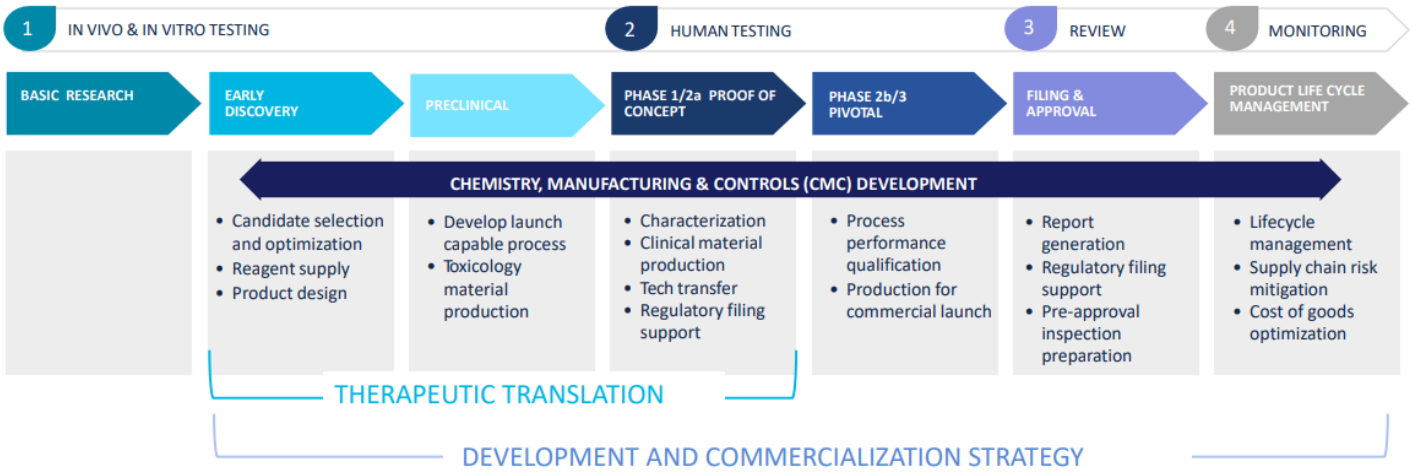

Fig. 1: A general CMC roadmap

Thus, it is important to build a detailed CMC roadmap that considers specific data your project will require, the experimentation necessary to create those data — including which stages of development will contain each action — and how everything fits within the available/planned timeline. Without expert input in this respect, sponsors often progress into pivotal studies before commercial process development is complete.

So, when preparing for commercialization, developers may discover manufacturing process changes are necessary, or that they lack some necessary analytical methods. Without those tools, they may encounter issues with the trial and/or interpretation of the clinical data. Being forced to implement significant process changes during pivotal studies, prior to going commercial, can greatly extend each study, as sufficient data must be gathered on the product after those changes have been implemented.

This due diligence too often must be weighed against the reality of the current funding environment, which pressures companies to achieve critical, short-term funding milestones quickly, prompting a rush on data-gathering and getting into the clinic. But it remains the sponsor's duty, assisted by its partners, to consider whether its actions are conducive to commercialization.

Early in a project, this can seem like a far-away problem, but both development and commercialization strategies require educated risk-taking, and calculating those risks accurately means considering the entirety of the project. Sponsors in a rush to advance a process that may not be reproducible or will not support the intended market may find that their product is not commercializable. A capable CDMO partner's role, especially for early-stage companies, is to ensure the data needed to support the eventual BLA filing are reflected in the clinical trials conducted along the way.

From a regulatory standpoint, regulators are actively working to establish a strong understanding of advanced therapies and can provide valuable insights and feedback. Therefore, sponsors may want to request an INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs) meeting with the FDA during the early stages of development. For that meeting to be as productive as possible, it is important to determine which data is needed from a CMC standpoint, both to guide the questions you will ask and to get meaningful feedback from the FDA. This methodical meeting pre-planning remains important throughout the pre-IND meeting, IND milestone meetings, and beyond (Fig. 2). Specificity allows the

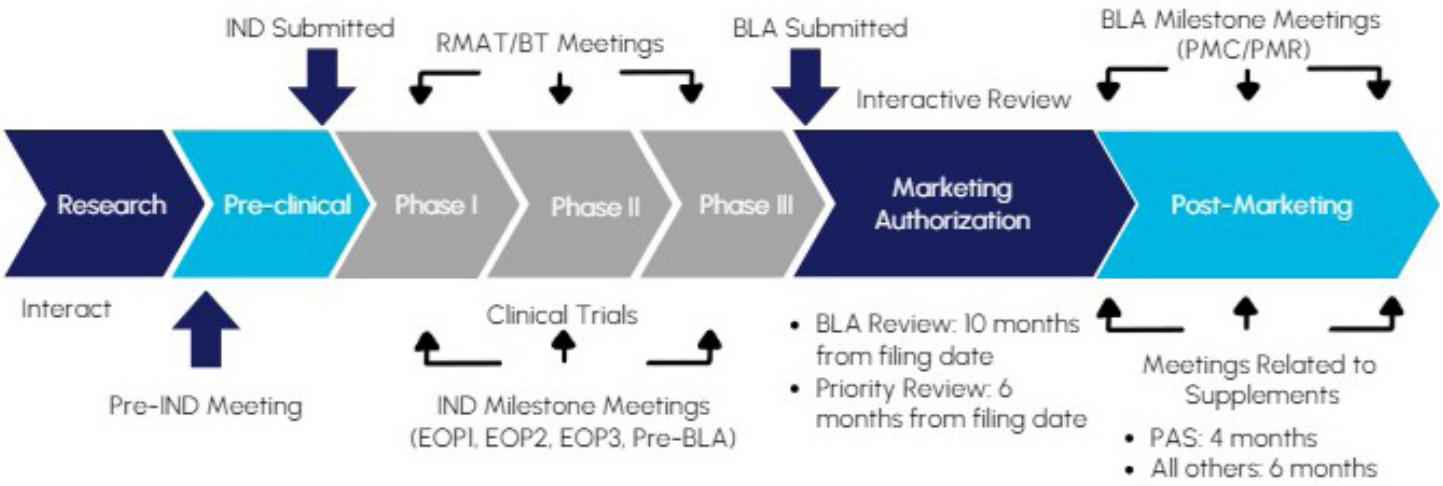

Fig. 2: FDA interaction

agency to be equally precise in responding to which parts of a strategy are acceptable and which are likely to encounter greater regulatory scrutiny.

Also, sponsors should not be shy about asking for additional meetings, but must be respectful of the agency's time: always have a set purpose and adequate data to support the discussion. Seeking general feedback that might otherwise be available through guidance documents or more public/academic sources is likely to result in rejected meetings. Moreover, those sources of information can point you toward the right questions to ask the FDA.

Transition to Commercial Goal Setting

Among the most difficult tasks in commercializing an R&D asset is shifting from expectations of basic research to phase-appropriate GMP manufacturing readiness. Thorough PD and analytical development (AD) will fill gaps in that understanding, but they often expose shortcomings in early-stage work that must be countered, as well.

For example, a research protocol may be followed early in development and the product may even be manufactured in limited quantities for early clinical studies, despite lacking a well-defined manufacturing process featuring established in-process controls and in-process testing. Analytical testing methods in use also may be insufficient to support an IND. In these scenarios, the CDMO's job is to guide the sponsor to a greater understanding of the additional controls or testing necessary to bolster its manufacturing process, making it robust enough to withstand FDA scrutiny.

Key to this effort is identifying and answering any questions relevant to process changes that may be necessary as production scales to commercial levels. For example, early-phase cell therapy activities in a research hospital might involve a lot of open manipulations in a biosafety cabinet. In a commercial setting, it is prudent to minimize those opportunities for human error or product contamination. The manner in which cultures are handled, the order in which the manufacturing process is executed, and even the product itself may need to change.

In this sense, development of advanced therapies is markedly different than that of small molecule products, which typically have well-defined CQAs. Changes to a small molecule manufacturing process between proof-of-concept data and commercial production can be readily supported through analytical testing of CQAs. However, with less-defined cell therapy

products, it is difficult to establish whether revamping some element(s) of production may have significantly impacted the product. And, due to the product not being as well understood, it is far more difficult to remediate product issues on the back end.

From an analytics standpoint, in cell therapy, CQAs often remain incomplete until the end of development, when more clinical data is available and clinical correlations can safely be made. Still, failure to collect enough data early, which can be studied and correlated once more information is gathered, is a common pitfall. In that same vein, basing decisions on a limited number of manufacturing lots risks an incomplete understanding of manufacturing variability. Although this generally affects gene therapy more than cell therapy, conducting all studies on one GMP lot, for example, inhibits researchers' ability to set accurate clinical specifications.

An Experienced Partner Translates the QbD Mindset into Action

Focusing on near-term milestones and objectives, without full consideration and understanding of actions that drive commercial success, can slowly undermine an advanced therapy development program. To that end, helping customers thoughtfully define their products and create bespoke CMC roadmaps is part of Landmark Bio's expertise.

Difficulty in establishing CQAs for complex biologic products can sometimes lead inexperienced advanced therapy developers to abandon QbD methodologies. However, it is precisely these types of programs where a disciplined approach to QbD can yield the greatest dividends. Developing effective control strategies requires product understanding, process understanding, and effective analytical tools to measure quality attributes. We support our partners by using QbD approaches to identify and prioritize development activities across each of these dimensions.

For example, there are times when closing gaps in product understanding is more important than launching into process optimization. Effective control strategies will ultimately combine process controls (critical process and material controls) and testing controls (robust analytical methods and sampling plans with defined in-process and release acceptance criteria) to ensure consistent product quality.

Finally, by implementing commercial discipline within advanced therapy programs, Landmark Bio helps ensure that documentation reflects the organization's accumulated knowledge on the product. Particularly in larger companies, knowledge possessed by the group handling one aspect of development is not always adequately passed on when the project advances to the next stage. Without thorough documentation, the understanding that drove prior steps, rationale for decisions, and thought processes can slip through the cracks. To learn more about how Landmark Bio can secure and accelerate your advanced therapy project, visit https://landmarkbio.com.

References

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About Landmark Bio

Landmark Bio is a cell and gene therapy manufacturing company focused on the development of innovative technologies, products, and services to bridge the gap from bench to patient.